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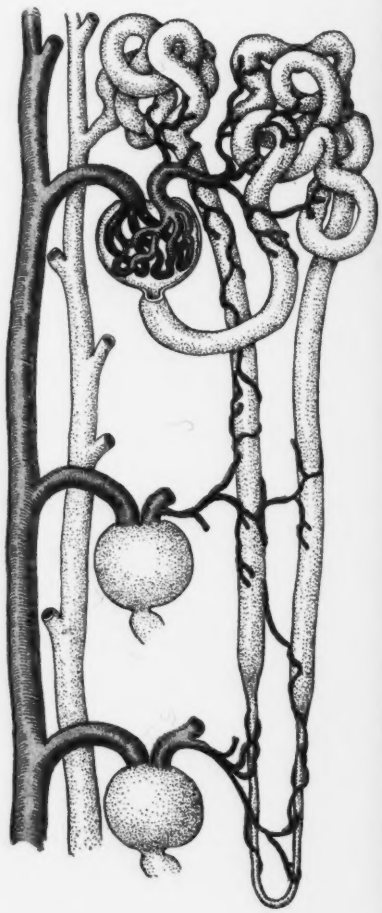

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Electric Instability of the Heart

The Concept of the Current of Oxygen Differential in Coronary Artery Disease

By BERNARD L. BROFMAN, M.D., DAVID S. LEIGHNINGER, M.D., AND CLAUDE S. BECK, M.D.

Normally oxygenated dog hearts and hearts rendered uniformly anoxic exhibit electric stability: there is no difference in resting electric potentials, and spontaneous ventricular fibrillation does not occur. When an area of myocardium is rendered ischemic, the resulting "trigger" may destroy the coordinated mechanism of the heart. A current of oxygen differential is produced across the zone of contact between red and blue myocardium resulting in "electric instability." In the electrically stable, uniformly anoxic heart, perfusion of an area with red blood produces a "reverse trigger" and electric instability. Application of these concepts and therapeutic implications to human coronary disease appears justified.

IN the vast majority of deaths due to coronary artery disease, the immediate cause of cardiac arrest remains obscure. In only a relatively small group can cardiac death be explained on the basis of the degree of reduction of total coronary inflow and extensive destruction of myocardium. These patients have "muscle death;" the heart becomes hypodynamic, and eventually fails.[1] Presumably, little can be accomplished with respect to protecting these patients from death. However, in the much larger group who die of "mechanism death," destruction of the coordinated heart beat occurs in a heart with adequate total coronary inflow and functional myocardium.[1] Such a catastrophe appears to be, to a large degree, preventable. Clinicopathologic studies such as those of Yater and co-workers[2] and Blumgart[3] confirm this concept of mechanism death in patients dying from coronary disease.

It has become increasingly evident that death in coronary disease is not so much due to reduction in total coronary inflow as to uneven or unbalanced distribution of the available supply. The development of adequate functioning intercoronary channels[4] serves to reduce this imbalance and gives protection against mechanism death. Methods which safely and effectively produce these channels should be applied to patients with coronary disease.

Trigger concept: In order to better understand the events leading to death in the presence of coronary disease, the concept of the *trigger* mechanism has been evolved. The *trigger* was originally defined as an ischemic area of myocardium capable of sending out impulses that in turn destroy the normal mechanism.[5] The addition of small amounts of blood to this area can obviate the destructive properties of the trigger. Extensive experimental and clinical experience with the surgical treatment for coronary artery disease has substantiated the concept of the trigger mechanism and has demonstrated the remarkably beneficial effect of a few cubic centimeters of blood delivered to a potentially ischemic area in preserving the coordinated mechanism and viability of heart muscle.[1, 6]

The present study is a preliminary attempt

This work was done in the laboratory of Dr. Claude S. Beck and supported by grants from the United States Public Health Service and the Cleveland Area Heart Society.

to define further the mode of production of the trigger area and mechanism death, and to evaluate the associated bioelectric phenomena. Experimentally, extensive studies have been carried out concerning the effect of various forms of "injury" on the heart. Coronary artery ligation has been considered the method par excellence for producing "injury." The area of ischemia, or trigger area, which results has certain electrophysiologic features. An "injured" region has been defined[7] as one which undergoes subnormal changes in the intensity of polarization owing to impairment of its ability to polarize or depolarize. During diastole, the "injured" area is electrically negative with respect to surrounding myocardium, having a more or less sharp boundary at the margin of the "injured" zone.[8, 9] During systole the "injured" area may be electrically positive with respect to the "noninjured" muscle.[10]

The "current of injury" which results from this electric imbalance is manifested by deviation of the S-T segment of the electrocardiogram. The "injured" area is characterized by S-T segment elevation in direct leads derived from its surface and in indirect leads positively influenced by this area. Theoretically, areas adjacent to the injured area would be expected to exhibit S-T segment depression.[11]

Since "injury" as such rarely occurs clinically, and for reasons to be discussed later, we prefer to use the term "trigger" defined as an area of myocardium which is relatively ischemic with respect to contiguous better-oxygenated muscle; it is characterized by diastolic electric negativity and demonstrates S-T segment elevation in direct electrocardiographic leads from its surface.

Studies in this laboratory and others[12] have demonstrated that sudden perfusion of a previously occluded coronary artery frequently results in ventricular fibrillation and death of the animal. This observation suggested to one of us (C. S. B.) the theoretic possibility that the deleterious effects of the trigger were produced by a marked difference of oxygen content on either side of an area of contact; this zone may be static and well defined or may be rapidly undergoing change in position.

Concept of reverse trigger: Total anoxia (or asphyxia), although the most advanced form of "injury" of the heart, does *not* cause ventricular fibrillation. We will explore the theoretical proposition that perfusion of one coronary artery with oxygenated blood during total anoxia will cause a previously "electrically stable" heart to develop the characteristics of a trigger in the anoxic muscle, and demonstrate "electric instability."

Materials and Methods

The observations herein presented were made during the course of thousands of operations on dogs carried out in the development of the present operative treatment for coronary artery disease.[1] Under ether or intravenous Nembutal anesthesia, the chest was opened via a left lateral incision. Respiration was maintained by means of the Rand-Wolfe respirator. The pericardium was opened and sutured to the chest wall as a cradle for the heart.

Methods for Producing Trigger Area

(1) Multiple small artery occlusion. Three or more small arteries usually supplying an area at the apex are ligated.[5] Through small cannulae inserted distal to the occlusion, blood may be perfused into the potential trigger area.

(2) Large artery occlusion. The left descending or circumflex artery is cannulated near its origin (fig. 1). Perfusion is maintained via a cannulated carotid

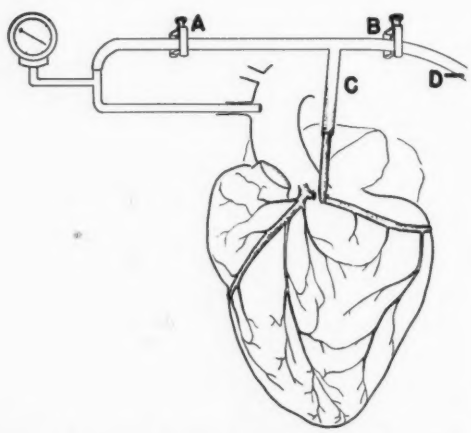


Fig. 1. Perfusion system for left circumflex coronary artery. With clamp A open and clamp B closed, distal artery is perfused via the carotid artery. With clamp A closed and clamp B open, distal artery is perfused from pressure bottle at D. Clamping of tubing at C produces complete circumflex occlusion.

artery.[13] The trigger is produced by clamping the perfusion system to the test artery.

(3) Reduced perfusion. Instead of complete occlusion of the test artery, it is perfused from a reservoir with one of the following: A. Venous blood previously collected under oil from the animal. B. Anemic blood in which the hemoglobin concentration is reduced by dilution with plasma or saline. C. Oxygenated blood under reduced perfusion pressure, at a reduced rate of flow.[14]

Production of reverse trigger: Generalized myocardial anoxia may be induced by simply clamping the tracheal tube and progressively asphyxiating the animal. The test artery is then perfused with oxygenated blood from a pressure bottle at a mean pressure of 100 mm. Hg. Myocardial anoxia may also be produced by allowing the animal to rebreathe to any desired oxygen concentration (5 to 10 per cent oxygen) in the inspired air, the carbon dioxide being absorbed by soda lime. An alternate method for regulating the inspired air is to control the oxygen concentration via the anesthesia machine. The use of regulated anoxia rather than asphyxia obviates the many other secondary factors produced by asphyxia, including the effects on the cardiac and respiratory centers.

Electrocardiographic studies. These were carried out by employing condenser-coupled, amplifier-type direct writers. Usually a Sanborn Viso-Cardiette or 4-channel electrocardiograph was used, the latter permitting simultaneous tracings from indirect as well as direct epicardial leads at normal paper speeds and at speeds of 50 mm. per second (twice normal). The direct epicardial or sweep electrode consisted of a saline-soaked cotton-tipped "V" lead. This electrode was applied to the epicardium and swept across designated areas during continuous recording. The sensitivity of the epicardial lead was reduced to 1/10 to 1/20 of standard because of the much higher voltages existing at the epicardial surface. This sweep electrode was found to produce no pressure effect upon the epicardium and when it was swept across the epicardial surface the isoelectric line remained remarkably stable.

Usually one of the limb leads was recorded at standard sensitivity before or after the epicardial lead when the single channel recorder was used. The 4-channel apparatus permitted simultaneous recording of the following: (1) an esophageal lead at the level of the apex; (2) an intracavitary lead using an electrode-tipped cardiac catheter inserted via the left atrial appendage; since introduction into the left ventricular cavity usually provoked intermittent premature ventricular beats, this electrode was usually withdrawn to the mitral orifice; (3) a unipolar limb lead, usually aV_F; (4) a direct epicardial sweep lead.

Control tracings were made before and after each procedure. In most cases, the various procedures were performed repeatedly to demonstrate the reproducibility and the reversibility of certain findings.

Results

Figures 2 to 6 demonstrate typical electrocardiographic observations during the various studies.

Control Studies

Sweep epicardial leads, whether from base to apex (fig. 2) or from descending coronary area to circumflex (fig. 5), exhibited the same general characteristics over the surface of the left ventricle. The height of the R wave varied somewhat over the precordium; in some instances it appeared constant over the area of exploration (fig. 6). The R wave was always followed by a well-defined S wave. The S-T segment was usually isoelectric or slightly elevated and was followed by a rather deeply inverted T wave. In general, the ST-T segment was definitely depressed.

Generally, there was little significant change in the unipolar limb leads after the chest and pericardium were opened. In aV_F, the QRS was almost invariably upright. The S-T was isoelectric, followed by an inverted T wave (fig. 5).

The esophageal lead, with the electrode placed at the level of the apex, showed a Q wave with a fairly tall R, isoelectric S-T and inverted T wave (fig. 5). The intracavitary lead revealed a pure QS wave with a slightly elevated or isoelectric S-T segment and small, upright T wave (fig. 5). This is similar to intracavitary leads from the left ventricle reported by others.[15-17]

Repeat control studies after ligatures were placed in position around test arteries showed no significant change. Following cannulation and perfusion of the test artery via the carotid, there was also no significant change, nor did constant perfusion of the test artery from the pressure bottle at a mean pressure of 100 mm. Hg alter the electrocardiogram (fig. 5).

Effects of Multiple Artery Occlusion

Sudden occlusion of multiple small arteries supplying a given area of myocardium was followed by the appearance, within 60 seconds,

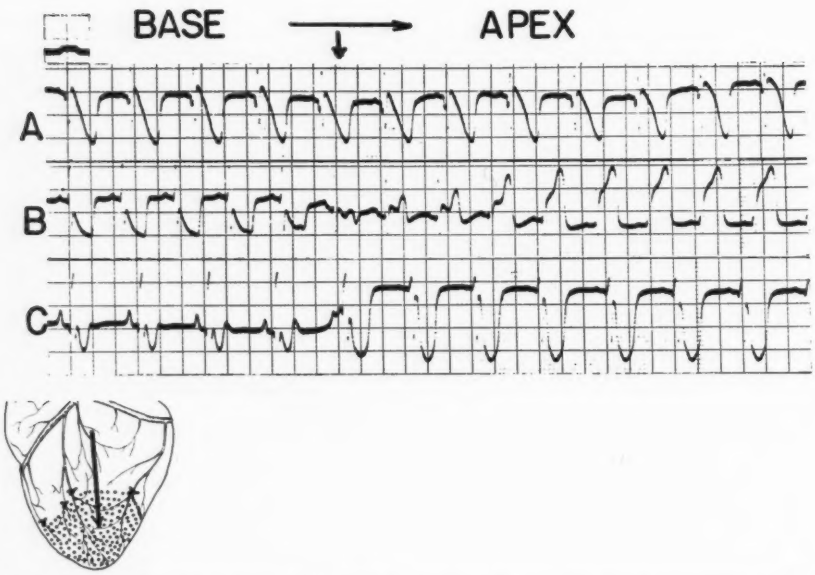


FIG. 2. Multiple ligation at apex. In this and subsequent figures, the insert represents the trigger area (stippled); the arrow shows the direction of the epicardial sweep lead. Sensitivity: 1 cm. = 15 mv.

A. Control. *B*. Trigger produced by multiple ligation at apex. S-T segment depression at base with abrupt transition to S-T segment elevation over cyanotic apex. *C*. Reverse trigger. Stippled area perfused via multiple cannulae with red blood at 100 mm. Hg from pressure bottle during asphyxia, so that surrounding muscle is deeply cyanotic after 5 minutes. Over base, ST-T segment not as depressed as in control; over pink area transition to marked ST-T depression. Note apparent shift in "isoelectric" line.

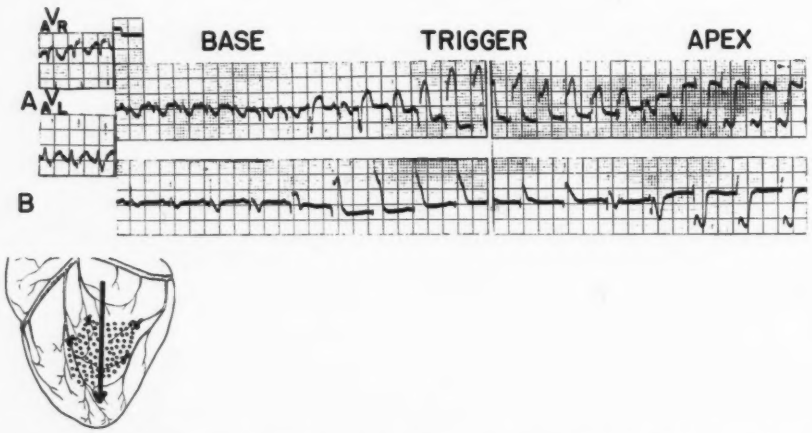


FIG. 3. Multiple ligation producing trigger area near apex, but leaving apex pink. Control omitted. Sensitivity: 1 cm. = 5 mv.

A. Stippled area cyanotic (trigger). Over pink base, no S-T segment depression. Marked S-T elevation over trigger with abrupt transition to S-T depression at pink apex. Lead aV_R shows S-T segment depression, aV_L shows S-T elevation. *B*. Asphyxia superimposed upon trigger. Entire heart now cyanotic to some degree. Although S-T segment deviations persist, they are not so marked.

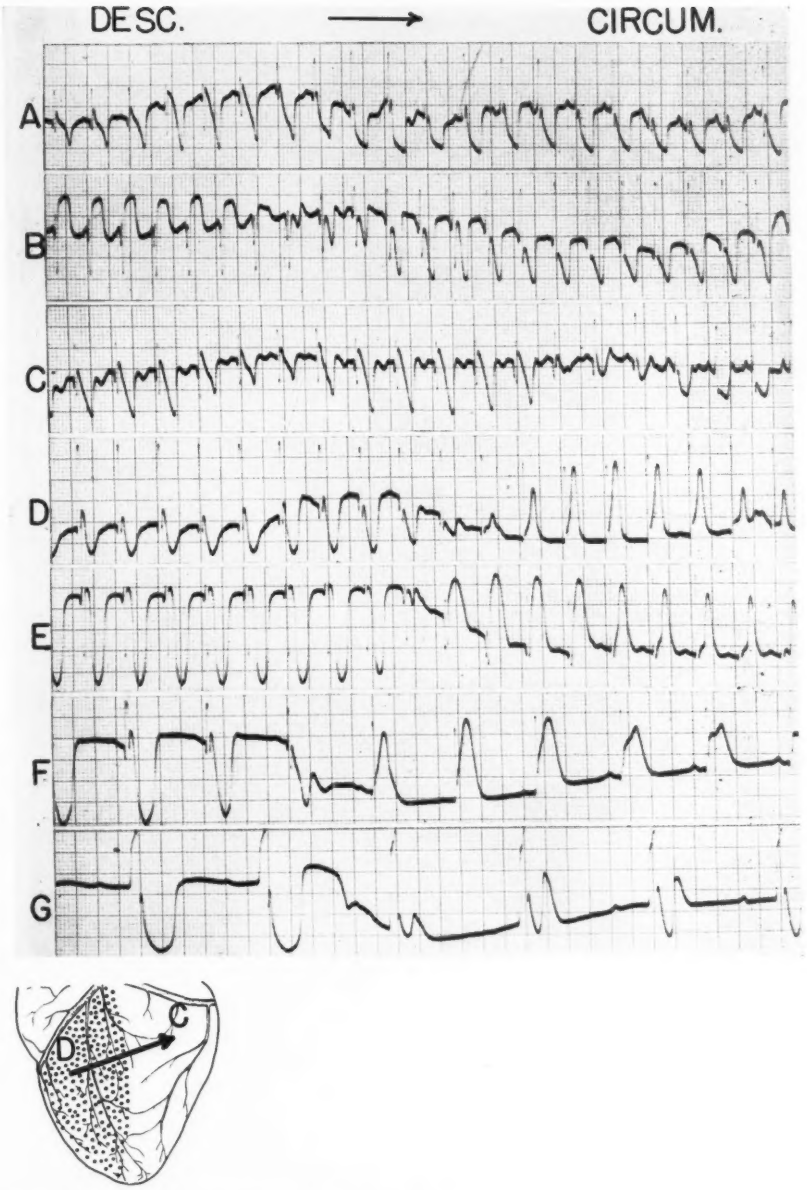
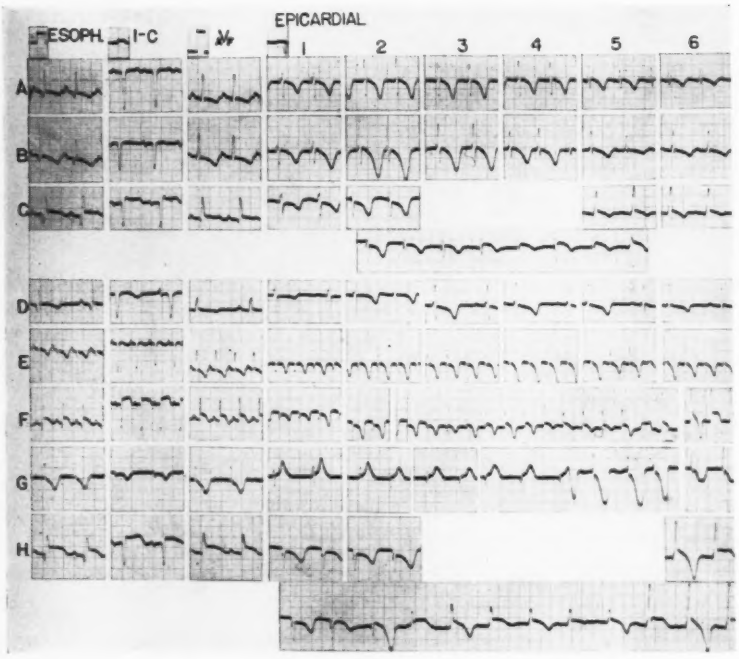


FIG. 4. Left descending artery perfusion. Epicardial sweep lead from descending (D) to circumflex (C) area. Sensitivity: 1 cm. = 15 mv.

A. Control. *B*. Occlusion of descending. Stippled area cyanotic (trigger). S-T segment elevation over trigger area with minimal S-T depression over pink area. *C*. Control, 30 seconds after *B*. *D*. Reverse trigger. Asphyxia for 2 minutes, perfusion of descending area with oxygenated blood for 2 minutes. Stippled area pink. Slight S-T segment depression near transition zone, with S-T elevation over cyanotic area. *E*, *F*, *G*. Reverse trigger at 3, 5 and 7 minutes. ST-T segment depression over pink area progressively pronounced.



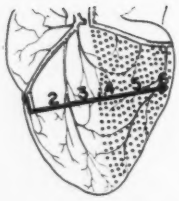
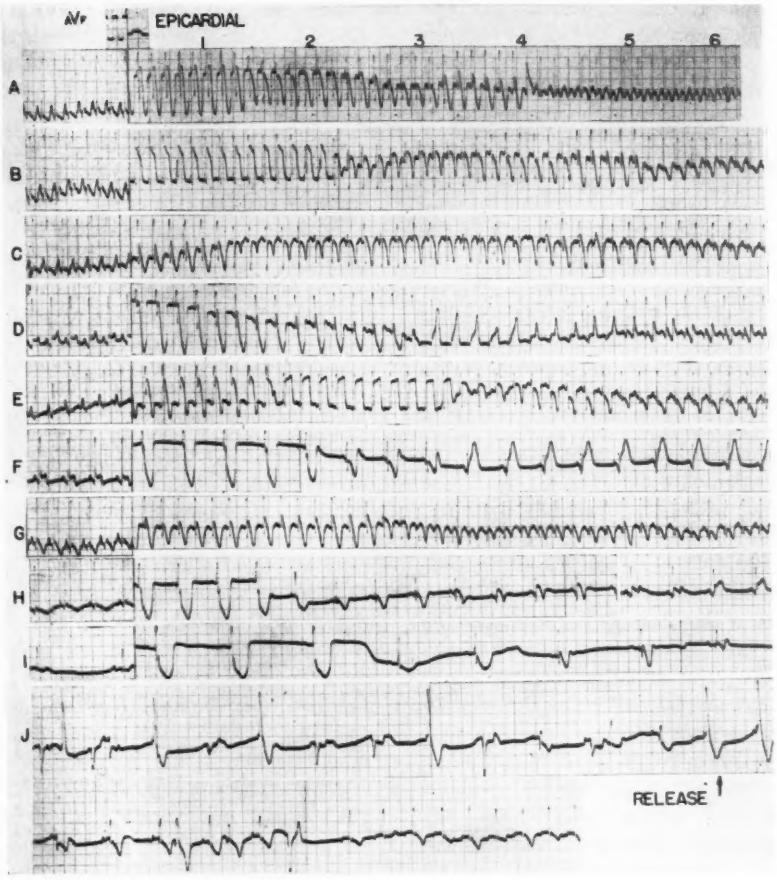


FIG. 5. Circumflex perfusion. Simultaneous 4-channel recording. Esophageal lead (esoph.) at apex. Intracavitary (I-C) lead at mitral orifice. Limb lead aV_F. Epicardial sweep lead (sensitivity: 1 cm. = 20 mv.) across positions 1 to 6 as designated on insert. Double speed (50 mm. per second) recording in *A*, *B*, *C*, *D*, *H*. In *C* and *H* extra inserts to show continuous sweep across transition zone.

A. Control, before perfusion. *B*. Circumflex artery perfused via carotid. Also no change when circumflex perfused from pressure bottle at 100 mm. Hg. *C*. Circumflex occlusion, 2 minutes. Stippled area cyanotic (trigger). S-T segment elevation in esophageal, intracavitary, and foot lead. Epicardial sweep shows S-T segment depression over the pink area with transition to S-T elevation over the trigger area. *D*. Total asphyxia—4 minutes. Except for the slower rate, there is no significant change from the control. *E*. Control (at normal paper speed). *F*. Circumflex perfused by desaturated venous blood from pressure bottle. Stippled area cyanotic. S-T deviations similar to those produced by trigger in *C*. *G*. Reverse trigger. Asphyxia for 6 minutes. Circumflex perfusion with oxygenated blood. S-T segment depression in indirect leads. ST-T elevation over cyanotic area with transition to ST-T depression over oxygenated (stippled) area. *H*. Circumflex occlusion (trigger) again. Indirect leads again show S-T segment elevation. S-T depression over pink area with transition to S-T elevation over trigger. (Note electric alternans, most obvious in epicardial leads over trigger.)



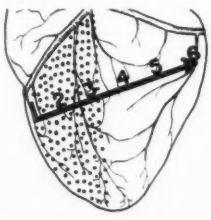


FIG. 6. Descending perfusion. Limb lead, aV_F and epicardial sweep lead (sensitivity: 1 cm. = 10 mv.) across positions 1 to 6 as indicated on insert. *A*. Control. *B*. Descending occlusion—45 seconds. Stippled (trigger) area cyanotic. S-T segment elevation over trigger area. No significant S-T depression over pink area. No change in foot lead. *C*. Asphyxia, 1 minute. No change from control. *D*. Reverse trigger. Asphyxia 2 minutes, descending perfusion with oxygenated blood 1 minute. Stippled area pink. ST-T depression over pink area, ST-T elevation over cyanotic area. Foot lead shows S-T segment elevation. *E*. Asphyxia, 2 minutes, descending occlusion one minute. Stippled area, slightly more cyanotic than surrounding muscle. S-T segment elevation over trigger area, slight S-T depression over less cyanotic area. Foot lead shows slight S-T elevation. *F*. Reverse trigger. Asphyxia, 4 minutes, descending perfusion with oxygenated blood, 2 minutes. Marked ST-T depression over perfused (stippled) area. ST-T elevation over cyanotic area. Foot lead shows S-T elevation. *G*. Control. *H*. Reverse trigger. Four minutes of asphyxia, 4 minutes of descending perfusion. Stippled area pink. Marked ST-T segment depression over pink area with ST-T elevation over cyanotic area. Foot lead relatively normal. *I*. Reverse trigger, 2 minutes after *H*. Marked ST-T depression over pink area. Only slight ST-T elevation over cyanotic area. *J*. Continuous record of foot lead immediately after *I*, showing development of prefibrillation stage during reverse trigger. Release of asphyxia and return to normal perfusion (arrow) is followed by recovery. (Note electric alternans during recovery.)

of a rather sharply defined, increasingly cyanotic area which appeared to lose its contractility. In some instances, ligation of every available branch immediately resulted in ventricular fibrillation.[5] Within 30 to 60 seconds the S-T changes associated with the trigger area appeared (figs. 2 and 3). Figure 2*B* demonstrates the change in the epicardial lead as the sweep is made from the pink base to the blue apex. At the base there is rather marked S-T segment depression, of uniform degree, until the edge of the cyanotic trigger area is reached. At the margin of the trigger area there is a sudden shift in the direction of the S-T segment from depression to isoelectric and then to elevation. The diastolic baseline (T-P segment) appears to have dropped 6 mm. in the transition (or equivalent to minus 9 mv.). The degree of S-T segment depression over the pink area and the elevation over the blue area are approximately the same, suggesting that the predominant factor in producing these ST-T changes is the diastolic negativity of the trigger area[8] and the relative positivity of the pink area. The maximal surface resting potential difference is approximately 9 mv. At deeper levels within the myocardium it is presumably progressively decreased but still elevated at the endocardium.[15, 17]

Production of a reverse trigger (fig. 2*C*) results in a gradual loss of contractility as the heart became more cyanotic except for the perfused apical area. The epicardial lead shows a rather isoelectric ST-T segment over the cyanotic base. At the margin there is a sudden rise of the diastolic baseline without a corresponding rise of the ST-T segment so that a depressed S-T segment appears to be almost entirely a measure of the difference (14 mv.) in resting diastolic potential across the marginal area.

In the case demonstrated in figure 3, multiple ligation produced a cyanotic area near the apex, surrounded by pink, normally contracting muscle at the base and at the apex (fig. 3*A*). The epicardial lead at the pink base shows no S-T depression. At the boundary zone the S-T segment becomes elevated and then falls as the boundary at the apex is reached, at which point marked S-T segment depression appears. Again there is an apparent shift in the diastolic baseline, particularly in the transition near the apex. Here the difference in the diastolic baseline is approximately 6 mv. which is also the average S-T elevation over the trigger and the depression over the pink apex.

When asphyxia is superimposed upon the multiple ligation trigger (fig. 3*B*) the pink area also becomes cyanotic so that there is not so great a degree of difference in oxygenation across the marginal area. By the same token, the degree of S-T segment elevation over the trigger is somewhat decreased.

Large Artery Occlusion

Within 30 to 60 seconds after ligation of the left descending or the left circumflex coronary artery the area supplied by the occluded artery becomes hypodynamic and increasingly cyanotic with a distinct boundary at the well-oxygenated myocardium. Figure 4 demonstrates changes in the epicardial lead when the left descending coronary was the test artery. Corresponding sweeps with the epicardial lead were made from the descending area to the circumflex area. Two minutes after the control tracing (fig. 4*A*), the typical electrocardiographic manifestations of the trigger area are present (fig. 4*B*). There is marked ST-T elevation over the cyanotic area with a sudden transition at the margin to S-T isoelectricity and then depression. After a control period, asphyxia, plus perfusion of the left descending with oxygenated blood produces a reverse trigger. At two minutes of this reverse trigger (fig. 4*D*) there is a tendency toward ST-T depression on the oxygenated side of the margin with ST-T elevation on the cyanotic side. The diastolic baseline appears to have dropped approximately 10 mv. With further maintenance of the reverse trigger, progressive changes occur so that at five minutes (fig. 4*F*), marked ST-T elevation is present over the trigger area, with an evident shift in the baseline of 15 mv. At seven minutes (fig. 4*G*), marked ST-T depression is present over the well-oxygenated area with only slight ST-T elevation over the trigger.

Figure 5 demonstrates typical electrocardiographic findings in a dog with the left

ircumflex as the test artery. Simultaneous sophageal, intracavitary, limb, and sweep leads re shown. Perfusion of the circumflex artery ia the carotid produced no significant change rom the control record (fig. 5*A*, *B*). Two inutes after circumflex occlusion (fig. 5*C*), -T elevation is present in the esophageal, ntracavitary and foot leads. The sweep lead hows S-T segment depression over the well-xygenated area, with transition to S-T elevation across the margin of the trigger. After a eturn to control conditions, total asphyxia or four minutes produces little alteration from he control record (fig. 5*D*). Perfusion of the ircumflex area at 100 mm. Hg pressure with venous blood produces similar electrocardiographic changes to those produced with complete occlusion (fig. 5*F*). When the circumflex is then perfused with well-oxygenated blood during complete asphyxia, reverse trigger changes occur (fig. 5*G*): there is S-T segment depression in the esophageal, intracavitary, and foot leads; S-T segment elevation over the cyanotic area with a transition to S-T segment depression across the margin of the well-oxygenated area. A complete reversal of these S-T segment changes follows a return to normal oxygenation with occlusion of the circumflex (fig. 5*H*). Electric alternans is seen to develop and is most obvious in leads over the trigger area.

Figure 6 demonstrates left descending perfusion. Lead aV_F is shown with the sweep leads. Within 45 seconds of descending occlusion, uniformly marked S-T segment elevation is present over the trigger area with a transition to slight S-T depression across the margin (fig. 5*B*). With generalized asphyxia (fig. 5*C*), there is again little change from the control until the descending is perfused with oxygenated blood (fig. 6*D*), at which time S-T segment elevation appears on the cyanotic side of the margin (and in the foot lead). Occlusion of the left descending during asphyxia (fig. 6*E*) produces S-T segment-elevation over the occluded area and S-T depression over the cyanotic but relatively better-oxygenated area. Production of a reverse trigger (fig. 6*F*) then demonstrates marked ST-T depression over the well-oxygenated descending area with a transition to ST-T elevation over the cyanotic area. The apparent fall in the diastolic baseline is approximately 12 mv. Following a control period (fig. 6*G*), a prolonged reverse trigger (fig. 6*H*) ultimately produces marked ST-T depression over the oxygenated area with little or no elevation over the cyanotic area (fig. 6*I*). Again marked shifts in the baseline occur. A continuous record (aV_F) then shows (fig. 6*J*) the onset of rapidly progressive ventricular ectopic activity, which is uniformly followed by ventricular fibrillation. In this instance ventricular fibrillation was prevented by a return to normal oxygenation and perfusion.

General Observations

Ligation of the left descending or circumflex results in ventricular fibrillation and sudden death in 50 to 70 per cent of the dogs subjected to this procedure. In dogs which do not fibrillate after 10 to 20 minutes of occlusion, sudden release of the ligature results in the onset of ventricular fibrillation in approximately 30 per cent of the animals in which this is done. Direct epicardial leads over the suddenly perfused area usually shows an immediate reversal of the S-T segment from elevation to depression.

In more than 50 dogs subjected to generalized anoxia (asphyxia), spontaneous ventricular fibrillation did not occur. Epicardial leads showed no significant S-T deviations. Death is accompanied by pacemaker failure or A-V conduction failure. Resuscitation can be accomplished readily with return to normal oxygenation.

In dogs rendered generally anoxic, perfusion of a coronary artery with oxygenated blood may induce ventricular fibrillation. As previously shown, S-T segment deviations appear only with the perfusion.

Discussion

Current of Oxygen Differential:

It has long since been demonstrated that "injury currents" may develop at the margin of infarcts with the result that the balance of electric potential difference in the heart as a whole is affected.[18] These "currents of injury" have been produced in many ways in the ex-

perimental animal. The simplest and commonest method is the production of an area of ischemia by complete large artery ligation. Partial ligation has also been used.[11] Direct injury to areas of heart muscle has been achieved by extremes of heat and cold, chemicals, pressure, the application of suction, and direct trauma to the myocardium. The direct application of these methods to human coronary disease has provided valuable physiologic and electrocardiographic information, but is misleading in some respects. "Injury" as such, does not occur in human coronary disease. Asphyxia, with generalized myocardial anoxia, is "injury" of the highest order, and yet no "current of injury" is produced. It is only when there is a relative reduction in the total injury, i.e., perfusion of part of the myocardium with oxygenated blood, that the so-called "current of injury" appears. Thus, it can be demonstrated that the electric manifestations of "injury" depend upon a *difference* in the degree of oxygenation of contiguous areas of myocardium.

Our studies have shown that this current is produced following large artery ligation and also multiple small artery ligation. The method of reduced perfusion, as shown in figure 5*F*, also produces currents when the degree of oxygenation of the perfused area is reduced to approximately 50 per cent of the normal perfusion.[14] (These studies will be described in a later publication.)

Suffice it to say, insofar as the human myocardium is concerned, it would appear that the "current of injury" is really a *current of oxygen differential* and depends upon the relative oxygenation in contiguous areas.

Measurement of Currents

Although it is not our purpose at this time to attempt to explore the various theoretic electrophysiologic considerations concerning the genesis of electrocardiographic changes associated with myocardial ischemia or "injury," a few observations are pertinent. Soon after obstruction of a coronary artery, the ischemic area of heart muscle becomes electrically negative with respect to the normally oxygenated muscle.[19, 20] According to Katz[21] the "injury currents" set up by damaged living tissue establish their own electric field independently of the fluctuating electric field produced by activation and restitution of the remaining heart tissue. The S-T segment is the measure of this electric field.

A potential difference exists at the boundary between well-oxygenated and poorly oxygenated muscle giving rise to a flow of current across the boundary and an associated electric field.[7, 15] Obviously, with our present method of recording, absolute measurements of change in electric potential cannot be made. (More extensive studies using a direct-coupled amplifier[22] are being carried out in an attempt actually to measure diastolic and systolic differences in potential produced by trigger areas.) Displacement of the S-T segment in these studies is then an approximate expression of the sum of the difference in electric potential existing during systole and diastole.

Production of Currents

Whether by larger artery ligation or by multiple ligations of small branches, a well-defined trigger could always be produced. Although S-T elevation occasionally appeared most marked in the center of the trigger area, usually there was no gradual or proportional fall as the margin was approached. As a matter of fact, approximately the same degree of elevation was maintained until the sudden change to isoelectric at the margin. In general, the most marked and abrupt S-T segment changes occurred with the multiple ligation technic of trigger production (figs. 2 and 3). In each such experiment there was an abrupt change from S-T segment elevation to S-T segment depression at the transition from trigger to normally perfused muscle. However, even in single artery ligation most frequently (although not always) there was also found some degree of S-T depression over the nonischemic area. This differs from the experience of Rakita and co-workers[15] who on no occasion found S-T segment depression on the anterior surface of the heart adja-

ent to the area of ischemia. Others[17] have ound it necessary to occlude small terminal ranches in addition to the large artery to roduce marked S-T segment elevation in the schemic area. Leads over "uninjured" regions how depressed or isoelectric S-T segments[11, 16]

It would appear that three factors are involved in determining the current production and the associated electrocardiographic changes: (1) The degree of difference in myocardial oxygenation in the trigger area and in the surrounding muscle; (2) The abruptness of the transition between the two areas and (3) The relative size of the trigger area.

Adequate multiple small artery ligation produces more complete anoxia of a trigger area than does large artery occlusion, since it stops all arterial inflow into the area. With large artery ligation, collaterals may bring in enough blood to the marginal areas so that there is no abrupt transition, and hence no sudden difference in potential at the margin. Even in normal dogs[1] backflow studies have demonstrated physiologically functioning collaterals. It would appear that the absence of marked S-T segment deviation in some studies is due to a poorly-defined margin between trigger and nonischemic myocardium. Further studies using backflow measurements are now being carried out in an attempt to correlate further electrocardiographic changes following artery occlusion with collateral circulation.

Even with multiple ligation, there may be no S-T depression over the normally perfused area. In figure 3*A*, the epicardial lead over the pink base showed no significant depression despite the marked S-T segment elevation over the trigger and the marked S-T depression beyond the trigger at the apex. This may be due to a more poorly defined basal margin of the trigger area, due, in this case, to ligation of only two of the three vessels supplying this area.

In all probability human myocardial infarction is more like the changes produced by the multiple ligation method in that the size and definition of the infarcted area is determined by poorly perfused small vessels and collaterals, with the final insult being occlusion or a reduction in perfusion of a large artery. In patients with adequate collaterals,[4] complete large artery occlusion may occur without myocardial infarction or trigger production.

There would appear to be many similarities between the current here produced and ordinary galvanic (battery) current. Electromotive force is a function of the nature of the two dissimilar materials in electrolytic contact. When the heart muscle is of uniform oxygenation, there is no difference in potential. However, as the difference in oxygenation across the zone of contact increases, voltage is produced. (Whether the difference in potential is directly related to the degree of difference in oxygenation is yet to be determined.) Furthermore, the greater the area of the trigger (within certain limits), the larger the circumference, and hence the larger the area of contact with surrounding myocardium. Since current (amperes) is a function of the area of contact between two dissimilar materials, it can be seen that the larger the area of the trigger, the more current flow. Also, since the trigger acts as a volume source, the current density at a given area of the margin would be greater with a larger source.

It would appear, however, from the standpoint of production of currents that there are certain limits of predisposition as regards size of the trigger area. The larger the trigger, the smaller the nonischemic area, so that when each is approximately the same in size, maximum contact exists. However, if the trigger extends to the base, a boundary may be lost.[17] It would appear, then, that a relatively larger trigger area would be associated with a greater current production than a smaller area, assuming an equally abrupt margin and difference in oxygenation. However, even a very large trigger might have little electric effect if collateral circulation precluded an abrupt transition at the margin. On the other hand, a small area rendered completely anoxic with an abrupt margin might have a marked electric effect.

If the degree of ischemia in the trigger area is uniform throughout, the degree of S-T segment elevation in epicardial leads should be

more or less uniform across the epicardium. Our studies do show relative uniformity except near the margin. This also differs from the observation of Rakita and co-workers.[15]

The degree of S-T segment elevation over a trigger area appears to be inversely related to the size of this area. The larger the trigger beyond a certain optimum size, the lesser the S-T segment elevation, and the more poorly defined the margin with the better oxygenated area. In clinical electrocardiography, this may account for the lack of S-T segment elevation in massive infarction.

These observations appear to be confirmed by the "reverse trigger" studies. Progressive generalized anoxia produces little or no S-T segment displacement. Perfusion of a large artery with normally oxygenated blood results in S-T segment elevation over the anoxic area with S-T depression over the oxygenated area. The degree of these changes also appears highly variable. The small oxygenated area in figure 2*C* exhibits marked S-T segment depression, while the comparatively massive anoxic area shows only a slight tendency to S-T elevation. In figures 4, 5 and 6, the oxygenated areas are larger but still small as compared with the anoxic areas, so that eventually the S-T segment depression in the perfused area is much more prominent than the S-T elevation across the margin. However, it should be emphasized that in the reverse trigger, as in the trigger, with the production of a difference in tissue oxygenation in contiguous areas, a difference in potential is present.

It has been demonstrated experimentally and in terminal electrocardiograms in man[23, 24] that conditions which produce gradual overall diminution in the functional capacity of the cardiac tissue without predisposition to ectopic ventricular systoles result in failure of the pacemaker or of A-V conduction, but very rarely induce ventricular fibrillation. In the studies herein presented, progressive generalized asphyxia or anoxia produced little or no significant change in the various electrocardiographic leads. *No* current of oxygen differential could be demonstrated and ventricular fibrillation did *not* occur.[25, 26] Total anoxia, although eventuating in cardiac arrest (as well as arrest of all other biologic processes), is, per se, not associated with ventricular fibrillation or sudden cardiac arrest. Furthermore, with return to normal oxygenation, the heart beat is readily restored.

Generalized asphyxia or anoxia produces myocardial injury of the highest order, yet "injury currents" do not exist. Despite the hyperexcitability which moderate anoxia produces,[27] it is only when a trigger or reverse trigger is produced that ventricular fibrillation and sudden death occur. In the presence of generalized anoxia, perfusion of one coronary bed with oxygenated blood, instead of being beneficial, may be catastrophic. The *current of oxygen differential* manifested by S-T segment elevation over the more ischemic area is shown to exist only when there is an abrupt transition between two areas having a difference in oxygen perfusion.

The S-T segment depression over the better oxygenated area and the S-T elevation over the trigger area are expressions of the difference in electrical potential existing across this zone. The trigger area is considered electrically negative to the better oxygenated part "and electric currents will flow until they equalize the potential difference. Hence an electric field will be established."[21] A condition of "*electric instability*" exists as a result of this current of oxygen differential.

In these experiments an electromotive force has been shown to exist across the margin of the trigger, manifested by S-T segment elevation on one side and/or S-T segment depression on the other side. This difference in potential is of the order of 5 to 20 mv. as measured at the epicardial surface. Deeper layers of the myocardium would be expected to record a lesser difference in potential.[15] The zone of difference appears to involve the endocardium, since endocardial leads also show S-T segment elevation immediately under the trigger area.[15, 17]

Ventricular Fibrillation

Ventricular fibrillation is associated with the onset of cardiac arrest in most deaths due to coronary disease. Other forms of cardiac arrest may occur. (A subsequent publication

vill demonstrate their similarity to ventricular ibrillation.) There is no evidence for the role of "intercoronary reflexes" in coronary deaths.[28]

The production of a trigger area, whether by multiple small vessel ligation or by large artery ligation, has been demonstrated to result in ventricular fibrillation and death. Trigger areas produced by the method of reduced perfusion within the limits of this study rarely caused ventricular fibrillation. The reverse trigger, when prolonged for an adequate period, frequently resulted in ventricular fibrillation. With all of these methods S-T segment deviations typical of currents of oxygen differential were produced. However, it is shown that ventricular fibrillation is most readily produced where the greatest degree of oxygen differential exists, namely, with complete ligation of arteries.

In 1943, Harris[12] demonstrated that ventricular fibrillation following coronary artery ligation was introduced by an accelerating series of premature beats. These ectopic discharges originate in the transitional zone and usually are followed by ventricular fibrillation within 10 minutes after artery occlusion. It was then suggested that the fundamental mechanisms that produce local discharges and fibrillation are identical in regional ischemia and galvanic stimulation. A strong, brief direct current shock has been shown to produce re-entry of impulses due to progressive decrease in the refractory period with a progressive increase in conduction time.[29] Repetitive accelerating discharges starting near the site of stimulation then initiate ventricular fibrillation. It has been demonstrated that the end of systole may be a particularly vulnerable period.[30]

An ischemic area of myocardium has a marked decrease in fibrillation threshold.[31] According to Harris[32] within a very thin sheet of boundary cells between ischemic and non-ischemic muscle there is a transition from adequately circulated cells to cells that are ischemic to a degree sufficient to produce complete inactivation. Exciting factors acting upon these hyperexcitable cells in the transition zone evoke discharges. Accelerating ectopic stimuli act to decrease the refractory period and slow conduction throughout the responding myocardium, predisposing to re-entry of impulses with subsequent ventricular fibrillation.[28]*

It would appear that there are two prerequisites for the initiation of ventricular fibrillation: (1) an area of myocardium which is particularly vulnerable, i.e., with a lowered fibrillation threshold and (2) an adequate stimulus acting upon this vulnerable area, such as a galvanic current.

Our studies appear to demonstrate that when adequate *currents of oxygen differential* act on an ischemic area of sufficient vulnerability, ventricular fibrillation is initiated. Harris[12] has suggested that "procedures which raise the galvanic fibrillation threshold should effect a protective influence against fibrillation following coronary occlusion, experimental or clinical." However, since these electric currents are shown to be produced by an abrupt difference in tissue oxygenation, it would appear that the most effective therapy would be to minimize these currents by the establishment of enough collateral circulation to prevent or reduce electric instability in any area. It is emphasized that any procedure which prevents "dry" areas following coronary occlusion will be effective far beyond the expectations based upon the small quantity of blood which will accomplish this.

Comments and Conclusions

(1) Mechanism death, which occurs in the great majority of coronary deaths appears to

* According to Katz[21]: "It has been considered that sporadic activity of an ectopic focus may be the result of the operation of injury currents acting as electric stimuli to initiate premature beats. Wherever heart muscle is injured the possibility exists of a greater than normal bioelectric current fluctuation developing during the heart cycle and this current may be sufficient in magnitude to stimulate adjacent muscle, especially if it is more excitable because of disease. It would have to be the fluctuation at the end of systole rather than the one at its beginning which acts as the stimulus since the heart would be refractory to the latter. The possibility of this mechanism giving rise to premature systoles is supported by the demonstration that premature beats arising during ischemia of the heart have their origin within or close to the ischemic area."

be due to the interaction of two factors: (1) a vulnerable area of ischemic myocardium (trigger) and (2) an adequate stimulus—the *current of oxygen differential*—produced by contiguous areas of myocardium of different degrees of oxygenation. This current in turn depends upon three factors: (1) the absolute difference in oxygenation of the two areas; (2) the abruptness of the transition from one area to the other and (3) the relative area of the trigger. These factors act to produce an electrically unstable heart. It is not to be assumed that ventricular fibrillation must occur when these currents are at their maximum. The amount of current necessary is determined by the threshold of the trigger area, so that fibrillation may occur when differences of potential are decreasing. Such factors as the accumulation of abnormal or excessive metabolites, changes in potassium concentration across the contact zone, and products of tissue necrosis undoubtedly play an intermediary role.

The relationship of these two factors, the current of oxygen differential and the fibrillation threshold, to the production of ventricular fibrillation may be expressed as the *Fibrillation Index*, that is:

$$\textit{Fibrillation Index} = \frac{\textit{Current of Oxygen Differential}}{\textit{Fibrillation Threshold}}$$

Thus, with a high fibrillation threshold, a large current is necessary to achieve the fibrillation index. By the same token the fibrillation threshold may be reduced to such a low level that a negligible stimulus may be sufficient to reach the fibrillation index. Agents such as hypothermia probably predispose to ventricular fibrillation by such a mechanism.[33]

In a potentially electrically unstable heart, even very small amounts of oxygenated blood delivered to the trigger area would be lifesaving. Functioning intercoronary channels reduce electric instability by modifying the above-named factors.

Yater's observations[2] are of particular significance in demonstrating the role of collateral circulation in preventing sudden death: In younger men the onset of the coronary attack occurs most frequently during strenuous activity. In the older patients, it occurs at rest. Unexpected death is more frequent in the young; longer survival following the acute coronary attack occurs in the older patients. We have shown that complete deprivation of blood supply to a given area is not necessary to produce electric instability. Only an adequate *difference* in oxygenation is a prerequisite. Ventricular fibrillation and sudden death may occur because one area of myocardium is well perfused during exercise whereas, because of perhaps a minor degree of arterial disease, the arterial supply to a contiguous area is not augmented, thus producing a difference in oxygenation. Ability to receive an augmented flow does not necessarily depend upon the larger coronary vessels. Disease may affect the smaller vessels as well. Coronary arterial resistance during exercise is probably reduced as a result of relative anoxia.[14] However, if the smaller vessels to a given area are unable to respond with vasodilatation while others are well perfused, a difference in oxygenation may again result in electric imbalance.

(2) The Beck I operation (abrasion of epicardium and lining of parietal pericardium, application of an inflammatory agent to these surfaces, and partial coronary sinus ligation) effectively produces intercoronary and extracoronary channels. Relatively small quantities of blood are involved in providing a more balanced distribution of available coronary artery inflow. The effectiveness of such a surgical procedure appears to lie in the prevention of the electrically unstable heart.

(3) It may be said that, within certain limits, the greater the difference in oxygenation the greater the electrical instability. Thus, in patients with generally lowered oxygenation of the myocardium (congestive failure, anemia, cor pulmonale) an area completely deprived of blood supply would not have as great a difference in oxygenation with respect to surrounding muscle and hence a lesser degree of electric instability. By the same token, if a patient with previously normal myocardial oxygenation develops an area of ischemia, the

administration of oxygen to this patient, rather than proving beneficial, may raise the oxygenation of the surrounding myocardium without penetrating to the trigger area, thus increasing the difference across the margin and predisposing to greater electric instability.

(4) Angina pectoris and pain associated with myocardial ischemia and infarction appear to be related to various degrees of electrical instability. Sudden death in a patient with angina pectoris may be due to production of an augmented current, without complete vessel occlusion. Coronary pain is not prominent in patients with generally poor myocardial oxygenation, such as in cyanotic congenital heart disease, cor pulmonale, and congestive heart failure. By the same token, angina of effort is not frequent. Presumably, even with the production of areas of anoxia, since the surrounding tissue is also poorly oxygenated, a marked difference of oxygenation does not occur.

(5) Any difference in oxygenation, whether it be over a well-circumscribed area or perhaps of a momentarily produced margin, may be catastrophic. It has been repeatedly demonstrated that when coronary ligation does not result in ventricular fibrillation, sudden release of the ligature may then produce fibrillation. Wolferth[11] also demonstrated that partial occlusion of a large artery is followed by S-T deviation in that area and then removal of the ligature produces sudden S-T depression. It appears that the sudden inflow of oxygenated blood into an ischemic area produces a current of oxygen differential, which, acting upon the relatively ischemic boundary cells results in fibrillation.

It is suggested that cardiac arrest in the operating room (or under other circumstances) might have a similar explanation. The myocardium of the anesthetized patient may be sensitized either by the anesthetic agent or other factors. Particularly during induction, sudden fluctuations in aeration of the lungs, blood pressure and coronary oxygen flow, acting on a sensitized heart, might produce these momentary boundary zones, with electric instability, and cardiac arrest.

Summary

The immediate cause of cardiac arrest in most deaths due to coronary artery disease is obscure. Experiments have been carried out to demonstrate that ventricular fibrillation and sudden death occur in a heart which is electrically unstable.

In the normal dog heart, electrocardiographic leads recorded across the surface of the left ventricle directly from the epicardium show uniform electric resting potential. It has been shown that ligation of a major coronary artery or multiple ligation of all smaller coronaries to a given area produces a "trigger" area which frequently leads to ventricular fibrillation, a break in the coordinated mechanism of the heart, and death. During diastole, these "trigger" areas are electrically negative to the normally oxygenated myocardium. During systole, this area may be electrically positive. This is best demonstrated by the epicardial tracings showing S-T segment elevation over the entire trigger area with a sudden change at the transition zone to isoelectric and depressed S-T segments over the normally perfused area. Measurements of electromotive force at the epicardium show differences in potential across the transition zone of the trigger area of approximately 5 to 20 mv. Thus, there is actually a flow of current (current of oxygen differential) producing electric imbalance.

This electric imbalance can be demonstrated in a reverse manner. Uniform anoxia is produced by asphyxia or other means. Despite the intense oxygen lack, ventricular fibrillation does not occur and the animals eventually die with an adynamic heart. Epicardial tracings in these animals show no electric imbalance. However, if during the course of generalized anoxia, normally oxygenated blood is perfused through one area of the myocardium, a "reverse trigger" is produced. That is, epicardial leads show the anoxic area to become suddenly negative to the oxygenated region, again with a difference in electric potential across the margin of the trigger. Only in such cases does ventricular fibrillation and sudden death occur. Thus it

has been demonstrated that this "trigger" which destroys the coordinated mechanism of the heart beat depends upon a difference in oxygenation of two adjacent areas of myocardium, and it is characterized by an associated difference in electric potential across the transitional zone.

Presumably, this marginal area is the true danger zone. Anoxia (and possibly other factors) render it vulnerable. The ectopic rhythms which lead to ventricular fibrillation have been shown to originate here. The marginal area is sharply defined electrically by the difference of potential across it. Thus, electric instability exists. It is this instability, due to an unequal distribution of coronary blood flow, which appears to be responsible for the majority of deaths in patients with coronary disease. A more nearly even distribution of coronary flow would prevent the formation of these trigger zones between anoxic and well oxygenated myocardium and thus maintain electric stability of the heart. Any procedure, such as the Beck I operation, which safely and effectively produces intercoronary channels, would tend to prevent or reduce this electric instability.

Further studies are now being conducted on various methods for producing and preventing electric instability. Accurate measurements of the currents of oxygen differential are being carried out.

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Summario in Interlingua

In cordes de can le quales es oxygenate de maniera normal e etiam in cordes de can le quales ha essite rendite uniformemente anoxic, il existe stabilitate electric: il non ha differentias del potentiales electric in reposo e nulle fibrillation ventricular occurre spontaneemente. Quando un portion del myocardio es rendite ischemic, le resultante "actionamento" pote destruer le mechanismo coordinate del corde. Un currente de differential oxygenic es producite a transverso le zona de contacto inter le myocardio rubie e le myocardio blau, e isto resulta in "instabilitate electric." In cordes que es electricamente stabile proque illos es uniformemente anoxic, le perfusion de un area partial con sanguine rubie produce un "retroactionamento" que etiam resulta in "instabilitate electric."

Omne differentia in oxygenation—non importa si illo involve un ben circumscripte area o forsan un margine de production momentari—pote devenir catastrophic. Il ha essite demonstrate repetitemente que si un ligation coronari non produce fibrillation ventricular, il pote occurrer que tal fibrillation resulta alora quando le ligatura es subitemente removite. Il pare que le subitanee influxo de sanguine oxygenate a in un area ischemic produce un currente de differential oxygenic que resulta in fibrillation per ager super le relativemente ischemic cellulas marginal.

Il pare justificate applicar iste conceptos e lor implicationes therapeutic a casos de morbo coronari in humanos.

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Some Clinical and Physiologic Effects of Mitral Commissurotomy

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Eighteen patients, selected for mitral commissurotomy on the basis of appreciable hemodynamic abnormalities as well as physical disability have been studied prior to and following surgery. The results suggest that well compensated patients with mitral stenosis, normal sinus rhythm and pulmonary hypertension are likely to benefit from operation. Patients with atrial fibrillation, good compensation and moderate pulmonary hypertension may benefit from mitral commissurotomy. In patients with atrial fibrillation, marked pulmonary hypertension and congestive heart failure, operation is hazardous and the likelihood of benefit is small. The importance of myocardial function in the production of these results is discussed.

WIDE variation in the clinical and physiologic observations in rheumatic mitral stenosis has often rendered difficult a balanced preoperative appraisal of the relative importance of myocardial function and valvular obstruction in the production of exertional dyspnea, fatigue and decreased ability to perform daily work. Since favorable outcome from mitral commissurotomy is largely dependent upon the accuracy of such an evaluation, the importance of developing broad frames of reference out of long-term, carefully controlled studies cannot be overemphasized. Equal in importance to patient selection is an assessment of the ultimate benefit accruing to properly selected patients, from mitral commissurotomy. As Soloff has suggested,[1] clinical observation bearing on this point is limited by the subjective nature of dyspnea, by the concurrent effects of vigorous medical therapy and by variations in the natural course of the disease. With a view to gaining information of a preliminary sort relative to both these problems, the data comprising this study were obtained.

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Clinical Material and Method of Study

During 1950 to 1953, 18 patients with chronic rheumatic heart disease and with mitral stenosis (group 1) as the predominating clinical feature were catheterized prior to, and following, mitral commissurotomy in accordance with a protocol described elsewhere.[2] All patients complained chiefly of exertional dyspnea but were free from edema, ascites, obvious hepatomegaly and pulmonary rales at the time of study, although 15 gave a history of having had hemoptysis, pulmonary or peripheral edema at some time in the past. By clinical and roentgenologic examination, all were free from obvious pulmonary disease and in all but three there was no clinical evidence such as a chronic, low grade fever or elevated erythrocyte sedimentation rate to suggest rheumatic activity during the preoperative studies.[11] All except one patient had moderate to marked cardiac enlargement on roentgen examination.[3] Fourteen patients demonstrated right ventricular hypertrophy on electrocardiographic examination, using the criteria of Sokolow and Lyon,[4] and in only one (case 11) was there electrocardiographic evidence of left ventricular hypertrophy.[5] Fluoroscopic examination failed to demonstrate left ventricular hypertrophy in any of the patients in this series. Ten patients had a normal sinus rhythm and in eight, atrial fibrillation was demonstrated. In addition to an apical murmur, suggestive of mitral stenosis in all patients, soft apical systolic murmurs were present in eight cases. In one additional case (E. C., case 16) the apical systolic murmur was prominent. All patients except E. C. were on digitalis and no patient was taking quinidine at the time of the preoperative study. All patients were considered suitable candidates for surgery on the basis of the clinical findings. In

TABLE 1—*Clinical Data*

Case No.	Patient	Status	Age	Cardiac Rhythm	Heart Size	MI	RVH Ecg	Failure		Digitalis	Quinidine	Interval
								Pre-existing	At time of study			
Group 1A												
1	G. K.	pre	30	NSR	16.0/11.2	0	+	+	0	+	0	4
		post		NSR	14.5/11.2							
2	W. M.	pre	47	NSR	13.1/11.7	0	+	0	0	+	0	3
		post		NSR	—							
3	C. G.	pre	30	NSR	14.7/12.0	0	+	+	0	+	0	8
		post		NSR	14.7/12.0							
4	R. D.	pre	24	NSR	15.4/12.5	+	+	0	0	+	0	9
		post		NSR	13.9/12.0							
5	H. T.	pre	44	NSR	15.5/11.9	0	+	+	0	+	0	12
		post		NSR	14.6/11.5							
6	D. B.	pre	23	AF	17.3/11.0	+	+	0	0	+	0	2
		post		AF	14.9/11.1							
7	H. R.	pre	36	NSR	16.5/12.4	+	+	0	0	+	0	19
		post		NSR	14.2/12.7							
8	N. Z.	pre	34	NSR	16.3/11.8	0	+	+	0	+	0	10
		post		NSR	—							
9	L. J.	pre	30	NSR	17.8/11.2	+	+	+	0	+	0	6
		post		NSR	16.2/11.5							
10	A. A.	pre	39	NSR	13.3/13.3	+	0	+	0	+	0	3
		post		NSR	11.4/13.3							
11	G. So.	pre	46	AF	17.8/12.9	0	+	+	0	+	0	3
		post		AF	—							
12	V. H.	pre	30	AF	17.0/11.2	+	+	+	0	+	0	2
		post		AF	—							
13	A. L.	pre	36	AF	14.1/11.8	0	0	+	0	+	0	9
		post		AF	15.2/11.6							
Group 1B												
14	J. A.	pre	27	AF	—	0	0	+	0	+	0	5
		post		AF	—							
15	A. M.	pre	41	AF	17.7/11.6	+	+	+	0	+	0	5
		post		AF	—							
16	E. C.	pre	24	NSR	17.0/11.4	+	+	0	0	0	0	4
		post		NSR	—							
Group 1C												
17	S. P.	pre	43	AF	16.8/12.6	0	0	+	+	+	0	3
		post		AF	15.5/12.6							
18	G. Sm.	pre	42	AF	17.8/11.5	+	+	+	0	+	0	4
		post		AF	19.4/11.5							
Group 2												
19	H. H.	pre	42	AF	13.3/14.3	0	+	+	+	+	0	—
20	F. T.	pre	42	AF	—	+	0	+	+	+	0	—
21	R. W.	pre	45	AF	16.2/11.2	0	+	+	0	+	0	—

Age: Age at time of study.

Heart Size: Ratio $\frac{\text{total observed transverse diameter, cm.}}{\text{predicted transverse diameter, cm.}}$ according to the Ungeleider-Clark Formula.

NSR: Normal sinus rhythm.

AF: Atrial fibrillation.

MI: Apical systolic murmur suggestive of mitral insufficiency.

RVH: Right ventricular hypertrophy.

Interval: Months intervening between operation and postoperative cardiac catheterization.

terms of reduced cardiac index or elevation of pulmonary artery pressure at rest or during exercise, all the patients in this series demonstrated one or the other, or both, of these abnormalities.

Three additional patients (group 2) were studied prior to mitral commissurotomy but did not survive the immediate postoperative period. All were patients with advanced rheumatic heart disease (class IV, according to the criteria of the New York Heart Association[6]) who had greatly enlarged hearts, atrial fibrillation and murmurs suggestive of mitral stenosis. Two of these three were in congestive failure at the time of study. The patients in this group were among the first in this institution to undergo mitral commissurotomy.

In each of the 21 patients in this series, the surgeon felt that an effective mitral commissurotomy had been performed.

Results

Following mitral commissurotomy the 18 survivors constituting group I were followed clinically and subdivided on the basis of clinical response. Sixteen of the patients stated that they had appreciable but varying degrees of relief from exertional dyspnea. In three of these patients, only subjective relief from exertional dyspnea was noted (group 1B), but the remaining 13 (group 1A) presented, in addition, objective improvement in the form of increased ability to perform daily work, increased exercise tolerance and gain in weight. In one of the latter (case 5) improvement was delayed by a postoperative recrudescence of rheumatic activity which did not subside until six months after the operative procedure. In two patients (group 1C) no change in either symptoms or signs was noted following the operation.

Good correlation exists between this clinical assessment and the physiologic data presented in table 2, where the observations prior to and following mitral commissurotomy are categorized in the following terms:

(1) *Cardiac Output and Pulmonary Artery Pressure.* Of the 13 patients in group 1A, the first six demonstrated an increase in resting cardiac output greater than 15 per cent, and a decrease in pulmonary artery mean pressure greater than 10 mm. Hg in comparison with the preoperative measurements. In the next five patients there occurred a decrease in pulmonary artery pressure of similar magnitude without marked change in resting cardiac output, while in the last two patients cardiac output was found to have increased appreciably without change in pulmonary artery pressure at rest, although one had less hypertension during exercise.

That the changes in cardiac output and pulmonary artery pressure in this group of patients are valid indices of physiologic improvement may be seen from a consideration of the data on oxygen consumption. In six patients (cases 1, 3, 5, 9, 12, 13) the pre- and postoperative oxygen consumption measurements are roughly comparable, and, with one exception (case 9), a significant increase occurred in cardiac output. In case 9 cardiac output remained approximately the same, but a significant decrease occurred postoperatively in pulmonary artery mean pressure. In case 11 the exercise cardiac output was greater and the pulmonary artery mean pressure was less than that noted preoperatively. In cases 6 and 10 there was an increase postoperatively in resting oxygen consumption, with cardiac output either the same (case 10) or proportionately increased (case 6). Improvement in these two patients was manifested by a decrease in resting pulmonary artery mean pressure, and, in case 10, by a decrease in this function in exercise in spite of a considerable increase in cardiac output.

The observations made on the three patients who alleged relief from dyspnea but in whom objective clinical benefit was doubtful or not observed (group 1B) are shown in table 2. In case 14 there occurred a barely measurable rise in cardiac output at rest, and in case 15, an appreciable decrease in oxygen consumption and cardiac output may well have caused the significant fall in pulmonary artery pressure that was observed. In case 14, the changes in cardiac output and pulmonary artery pressure are probably related to the changes in oxygen consumption. Aside from the fact that the changes in postoperative physiologic measurements in this small group of patients are modest, no clear pattern may be discerned. Clinically, cases 14 and 16 have developed cardiac failure since operation and case 15 ex-

pired in congestive heart failure, two years after the procedure had been performed. An autopsy was not obtained.

Finally, the two patients (group 1C), to whom no subjective or objective clinical benefit accrued, failed to demonstrate any real change in postoperative as compared with preoperative hemodynamic studies.

(2) *Ventilation.* In all except two patients in group 1A, resting ventilation was elevated during the preoperative study. Arterial hypoxia was not found in any patient in this group, nor was there any roentgen evidence to suggest pulmonary insufficiency or hemosiderosis. Postoperatively, five showed significant decreases in resting ventilation and the remainder were essentially unchanged. With the exception of case 14, the patients constituting group 1B and 1C failed to exhibit significant changes in resting hyperventilation in the postoperative as compared with the preoperative study. Estimation of alveolar ventilation of patients in whom the data were complete enough to permit calculation revealed the same trend towards reduction of ventilatory volume in improved patients following operation.

(3) *Heart Size.* Prior to operation cardiac enlargement was present in all patients studied. Following operation, 2-meter roentgenograms of the heart were obtained in 11 of the 18 patients who survived operation. Seven of the nine patients in group 1A in whom postoperative films were obtained demonstrated a decrease in heart size though none returned to the normal range, and in one patient (case 13) an increase in heart size was noted. Two of the five patients constituting groups 1B and 1C were studied with 2-meter heart films in the postoperative period. One of these demonstrated a decrease and the other an increase in postoperative heart size.

(4) *Atrial Fibrillation.* Atrial fibrillation was noted in 8 of the 18 patients constituting group 1 and in the three patients under consideration in group 2. Clinically, the patients with atrial fibrillation in group 2 suffered from advanced heart disease and had marked cardiac enlargement. Physiologically they tended to have very low cardiac indices and considerable elevation of pulmonary artery pressure. In addition the right ventricular end diastolic pressure at rest was elevated in two of the three patients. These three died shortly after operation in profound myocardial failure, exhibiting both peripheral shock and pulmonary edema.

In contrast, in patients in group 1 with atrial fibrillation, cardiac output, though reduced, tended to be higher than that noted in group 2, and only modest elevation of pulmonary artery pressure at rest was observed. The finding of only moderate elevation of resting pulmonary artery pressure in patients with atrial fibrillation has also been noted by Harvey and coworkers.[11] Indeed, exercise during the preoperative study was usually necessary to establish beyond question the existence of pulmonary hypertension. Four of these patients demonstrated objective clinical and physiologic improvement following operation, while in the remaining four, objective clinical improvement was not observed and physiologic changes, at best, were equivocal.

Comment

Correlation of the observations on cardiac output and heart size may offer some insight into the patterns of myocardial response to the surgical relief of valvular obstruction. Following mitral commissurotomy, five of the patients (cases 1, 4, 5, 6, 9) demonstrated an increase in cardiac output and a decrease in heart size.

In these patients, the rise in cardiac output resulted primarily from an increase in stroke volume, rather than from an increase in heart rate; this combination of an increase in stroke volume and a decrease in heart size suggests that cardiac emptying was more complete, following operation. In contrast, in the five objectively unimproved patients, stroke volume during the postoperative study usually was not increased relative to the preoperative measurement. Although the data do not elucidate the relative importance of improved left ventricular filling, decreased left atrial mean pressure or changes in intracardiac blood volume in effecting improved postoperative cardiac emptying,

TABLE 2—*Physiologic Data*

Case No.	Patient	Status	f		$\dot{V}_{E/M^2}$		R_E		$\dot{V}_{O_2}/\dot{V}_E$		$\dot{V}_{O_2/M^2}$		$CA_{O_2}-C_{VO_2}$		$\dot{Q}/M^2$		Heart Rate		Stroke Volume ml.		Sa_{O_2}		Pa_{CO_2}		pH		P.A. pressure s/d, m, mm.Hg		R.V. end-d, mm. Hg		R.A. m, mm. Hg	B.A. pressure s/d, m, mm.Hg	
			Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Exer.	Rest	Rest	Exer.
Group 1A																																	
1	G. K.	pre	19.0	—	4.92	—	0.78	—	38.6	—	154	—	5.6	—	2.75	—	72	—	55	—	95.7	—	35.1	—	7.46	—	140/44, 73	—	4	—	3	108/59, 75	—
		post	11.0	—	3.53	—	0.77	—	52.6	—	154	—	4.5	—	3.42	—	74	—	69	—	100.0	—	46.0	—	7.37	—	79/30, 44	—	2	—	0	126/66, 79	—
2	W. M.	pre	17.7	—	5.38	—	0.78	—	29.3	—	129	—	7.0	—	1.84	—	78	—	37	—	93.6	—	39.5	—	7.41	—	72/26, 45	—	3	—	—	106/65, 78	—
		post	14.0	19.5	4.13	7.70	0.77	0.84	35.0	38.2	118	240	5.1	6.7	2.31	3.58	58	76	70	82	97.0	97.0	36.0	38.5	7.44	7.41	36/14, 20	61/21,33	3	3	3	106/58, 75	141/67, 89
3	C. G.	pre	20.0	—	4.21	—	0.66	—	38.6	—	134	—	5.9	—	2.27	—	71	—	55	—	93.8	—	42.0	—	7.43	—	47/24, 30	—	0	—	—	118/66, 85	—
		post	23.3	—	4.50	—	0.76	—	35.9	—	132	—	4.6	—	2.87	—	72	—	72	—	97.6	—	42.5	—	7.40	—	28/11, 17	—	1	—	2	132/79, 99	—
4	R. D.	pre	12.7	21.5	5.10	11.93	0.82	0.86	33.5	32.5	139	316	6.6	13.9	2.11	2.27	80	144	42	25	97.6	97.0	—	—	—	—	59/35, 42	104/63, 84	—	—	0	95/63, 73	110/71, 82
		post	15.3	20.0	3.25	8.62	0.76	0.92	45.3	42.6	122	304	4.4	8.4	2.77	3.62	80	110	57	54	96.2	96.2	36.0	34.0	7.45	7.43	34/18, 25	71/43,54	3	2	—	94/58, 69	116/70, 84
5	H. T.	pre	18.3	—	5.84	—	0.76	—	31.0	—	151	—	7.7	—	2.03	—	78	—	40	—	94.7	—	45.0	—	7.35	—	74/31, 46	—	−1	—	—	118/67, 88	—
		post	9.0	—	3.13	—	0.75	—	55.3	—	144	—	4.1	—	3.50	—	78	—	74	—	95.8	—	48.0	—	7.39	—	40/18, 23	—	0	—	—	130/71, 88	—
6	D. B.	pre	16.0	—	3.94	—	0.79	—	34.3	—	111	—	8.3	—	1.30	—	63	—	34	—	97.2	—	46.0	—	7.34	—	51/25, 34	—	3	—	5	114/75, 85	—
		post	13.3	—	3.95	—	0.77	—	40.3	—	131	—	6.6	—	1.98	—	44	—	64	—	94.4	—	38.0	—	7.40	—	35/11, 19	—	4	—	4	108/79,89	—
7	H. R.	pre	9.8	19.0	4.13	19.1	0.72	1.01	43.9	23.4	149	367	7.0	14.8	2.12	2.48	80	133	44	31	—	—	—	—	—	—	69/30, 43	—	—	—	—	127/79, 101	—
		post	7.7	—	3.09	—	0.74	—	46.4	—	120	—	6.9	—	1.73	—	76	—	38	—	98.5	—	35.0	—	7.47	—	26/13, 18	—	—	—	—	104/55, 73	—
8	N. Z.	pre	11.0	—	4.37	—	0.72	—	45.7	—	165	—	4.7	—	3.51	—	71	—	85	—	96.1	—	40.0	—	7.43	—	52/27, 35	—	−2	—	−2	97/57, 72	—
		post	15.3	22.5	4.58	7.81	0.76	1.00	41.0	38.5	155	389	4.2	6.2	3.70	6.30	69	90	93	121	94.6	96.7	42.0	38.0	7.41	7.40	20/6, 10	45/17, 28	0	+8	0	108/58, 78	155/83, 108
9	L. J.	pre	23.3	—	4.50	—	0.75	—	34.8	—	129	—	3.6	—	3.59	—	68	—	81	—	99.0	—	41.0	—	7.40	—	63/26, 40	—	2	—	−2	—/—, 109	—
		post	16.7	—	4.19	—	0.78	—	39.6	—	135	—	3.7	—	3.67	—	68	—	85	—	97.0	—	39.0	—	7.44	—	41/19, 27	—	2	—	0	115/57, 75	—
10	A. A.	pre	—	—	3.51	5.73	0.81	0.82	38.7	43.7	120	220	4.2	6.8	2.84	3.24	77	96	66	60	96.8	97.4	—	—	—	—	37/23, 30	62/30, 45	—	—	—	118/73, 92	128/75, 97
		post	14.3	22.0	3.65	15.72	0.77	1.10	43.8	32.2	131	415	4.7	7.2	2.79	5.77	81	120	62	87	96.5	—	—	—	—	—	26/8, 15	50/26, 32	—	—	—	122/73, 95	—
11	G. So.	pre	12.3	19.4	4.20	7.75	0.85	0.77	39.8	46.8	147	319	5.6	10.9	2.63	2.93	85	114	55	46	95.2	95.8	41.0	40.5	7.43	7.41	37/19, 29	53/29, 41	1	—	—	132/84, 102	137/88, 109
		post	12.3	23.5	3.54	9.18	0.76	0.88	42.1	43.2	124	329	5.5	8.7	2.25	3.78	88	116	45	57	93.6	93.4	—	—	—	—	26/13, 18	40/19, 27	—	—	—	131/83, 103	135/88, 106
12	V. H.	pre	7.0	23.0	4.18	5.72	0.79	0.70	40.5	43.9	140	207	6.7	8.2	2.08	2.52	58	92	51	39	—	—	—	—	—	—	32/16, 20	67/40, 49	5	—	6	114/73, 89	120/82, 100
		post	—	—	3.22	6.00	0.74	0.78	53.3	45.0	141	222	5.7	7.5	2.47	2.96	70	93	51	46	—	—	—	—	—	—	29/15, 19	41/24, 30	—	—	—	116/71, 89	120/85, 100
13	A. L.	pre	13.7	15.0	3.70	6.89	0.81	0.88	40.3	41.8	123	237	6.3	7.8	1.95	3.04	45	78	66	59	98.2	95.4	35.5	37.5	7.49	7.45	28/11, 17	41/20, 29	1	—	0	106/65, 78	—
		post	9.0	—	3.09	7.35	0.74	0.82	50.1	50.4	128	307	4.2	6.5	3.05	4.73	64	90	72	80	94.1	94.6	40.5	—	7.41	—	26/12, 16	39/25, 31	3	5	—	106/58, 75	141/67, 89

Group 1B

14	J. A.	pre	13.0	—	6.32	—	0.72	—	33.6	—	175	—	7.2	—	2.43	—	70	—	60	—	99.0	—	33.0	—	7.49	—	37/20, 28	—	3	—	3	120/83, 90	—
		post	10.0	—	4.22	—	0.73	—	48.0	—	167	—	5.8	—	2.88	—	83	—	68	—	99.1	—	33.5	—	7.48	—	34/20, 27	—	5	—	4	123/88, 103	—
15	A. M.	pre	15.3	—	4.09	—	0.76	—	45.0	—	155	—	6.6	—	2.35	—	57	—	62	—	95.2	—	44.5	—	7.46	—	49/25, 32	—	4	—	6	88/54, 66	—
		post	14.0	—	4.11	—	0.83	—	40.9	—	138	—	6.8	—	2.03	—	55	—	59	—	95.2	—	38.0	—	7.46	—	33/15, 22	—	2	—	0	100/57, 71	—
16	E. C.	pre	13.0	23.0	4.80	11.8	0.89	0.81	30.4	38.3	121	372	7.0	12.6	1.73	2.95	79	112	37	45	—	—	—	—	—	—	75/43, 54	110/63, 79	—	—	—	115/75, 90	130/85, 98
		post	—	—	4.08	8.97	0.72	0.84	45.6	38.5	154	286	7.9	11.4	1.95	2.51	85	114	39	37	—	—	—	—	—	—	76/39, 54	118/68, 86	—	—	—	110/71, 87	148/88, 109

Group 1C

17	S. P.	pre	20.7	43.0	4.54	10.43	0.79	0.85	35.3	33.5	132	288	6.3	10.0	2.10	2.88	48	72	75	68	97.5	96.6	33.0	33.5	7.50	7.50	23/10, 13	45/24, 32	5	11	5	116/64, 82	140/81, 101
		post	19.7	27.7	4.75	12.41	0.74	0.90	35.6	33.5	139	338	6.6	11.7	2.10	2.89	56	80	64	61	96.8	97.8	35.5	34.0	7.45	7.43	18/9, 13	39/20, 28	—	—	3	143/88, 110	168/92, 120
18	G. Sm.	pre	13.8	—	4.29	—	0.78	—	33.7	—	118	—	9.3	—	1.28	—	44	—	47	—	98.0	—	37.0	—	7.47	—	40/17, 22	—	—	—	—	123/68, 82	—
		post	14.0	—	4.74	—	0.79	—	33.7	—	130	—	8.1	—	1.61	—	66	—	44	—	92.8	—	35.0	—	7.45	—	45/20, 28	—	7	—	5	125/76, 92	—

Group 2

19	H. H.	pre	14.0	25.0	5.62	9.88	0.81	0.83	26.8	23.3	133	203	7.9	10.8	1.68	1.88	85	102	32	31	—	—	—	—	—	—	86/45, 61	104/51, 68	6	—	—	101/72, 83	111/76, 87
20	F. T.	pre	18.3	28.0	5.77	10.78	0.70	0.90	34.9	27.3	178	259	8.1	12.0	2.18	2.16	96	135	35	24	—	—	—	—	—	—	90/47, 62	128/73, 95	7	—	—	125/80, 96	133/89, 98
21	R. W.	pre	18.0	—	5.29	—	0.69	—	34.7	—	151	—	10.6	—	1.43	—	80	—	27	—	—	—	37.0	—	—	—	109/49, 72	—	4	—	8	140/97, 117	—

f = Respiratory rate, breaths/minute.
$\dot{V}_{E/M^2}$ = Ventilation, liters/minute/square meter body surface area.
R_E = Respiratory quotient.
$\dot{V}_{O_2}/\dot{V}_E$ = Milliliters oxygen utilized per liter of ventilation.
$\dot{V}_{O_2/M^2}$ = Oxygen consumption, milliliters/minute/square meter body surface area.
Ca_{O_2}-C_{VO_2} = Arteriovenous difference, volumes per cent.
$\dot{Q}/M^2$ = Cardiac index, liters/minute/square meter body surface area.
Sa_{O_2} = Arterial oxygen saturation.
Pa_{CO_2} = Partial pressure of carbon dioxide in arterial blood.
P.A. Pressure = Pulmonary artery pressure.
R.V. end-d = Right ventricular end-diastolic pressure.
R.A. m = Right atrial mean pressure.
B.A. Pressure = Brachial artery pressure.

they do emphasize the importance of the overall myocardial response to the mechanical improvement wrought by mitral commissurotomy as a major determinant of the degree of clinical and physiologic improvement that follows the operation.

The mild elevation of the mean minute volume of pulmonary ventilation, seen in all patients prior to operation, has been noted previously by West and associates[2] and by Williams.[10] The reduction, postoperatively, in resting ventilation in many of the improved patients and the absence of change in the unimproved group is also noteworthy, but unexplained. It does not seem to be related to elements known to regulate ventilation; arterial oxygen saturation following operation in both improved and unimproved patients was essentially unchanged. No trend was apparent among the postoperative variations in arterial pH or carbon dioxide partial pressure in the improved group and, hence, the changes noted in these measurements were probably results of, rather than causes for, reduction in ventilation. Correlation with improvement in cardiac output or reduction in pulmonary artery pressure was also poor. Although the influence of changes in the physical properties of the lung resulting from commissurotomy was not evaluated, Saxton's study[9] suggests that compliance, at least, does not change. Thus, it would appear that an effective mitral commissurotomy may in some way affect a neurogenic integrating mechanism that governs ventilation but the pathway through which this influence is exerted is by no means clear.

Patient Selection

When the clinical and physiologic data are reviewed in an effort to obtain information which would be useful in the selection of additional patients for operation, three groups of cases may be clearly distinguished.

The patients with mitral stenosis as the major clinical feature who have normal sinus rhythm and pulmonary hypertension seem quite likely to derive benefit from mitral commissurotomy. Nine of the 13 improved patients were in normal sinus rhythm and all demonstrated clinical and physiologic benefit. This is in agreement with the experience of Werkö[7] and others.[8] The only unimproved patient with normal sinus rhythm had an appreciable degree of mitral insufficiency and, in retrospect, operation should not have been offered.

The three patients under consideration in group 2 with far advanced disease all demonstrated atrial fibrillation, very low cardiac output and considerable pulmonary hypertension associated with congestive failure. Postoperatively, these patients quickly developed more severe congestive heart failure and expired.

The eight patients in group 1 with atrial fibrillation all demonstrated essentially similar clinical and physiologic findings; all had mitral stenosis, cardiomegaly, six had histories of pulmonary edema, all were on digitalis and, physiologically, all exhibited reduced cardiac output and mild elevation of pulmonary artery pressure. They differed significantly from patients in group 2 in that resting pulmonary artery pressure was normal or only moderately elevated and in that they were not in congestive failure. Among these eight patients, however, nothing was found in the clinical or physiologic data which would have enabled the clinician to differentiate those who would derive benefit from mitral commissurotomy from those who would not; they remain as a problem to which no ready answer is available.

Summary and Conclusions

(1) Eighteen patients, selected for mitral commissurotomy on the basis of appreciable hemodynamic abnormalities as well as physical disability, have been studied prior to and following surgery.

(2) Of these, 13 exhibited postoperatively objective as well as subjective clinical evidence of improved cardiocirculatory function. Three alleged subjective improvement, although objective clinical evidence was lacking and two were clearly unimproved.

(3) When unequivocal objective clinical improvement was observed following mitral commissurotomy, physiologic study of 13 improved patients demonstrated an increase in cardiac output and a decrease in pulmonary artery mean pressure in six, a decrease in pulmonary

artery mean pressure without marked change in cardiac output in five patients and an increase in cardiac output without appreciable change in pulmonary artery mean pressure in two.

(4) Prior to operation, resting ventilation was elevated in all patients. Postoperatively, five improved patients demonstrated significant decrease in resting ventilation and the remainder were essentially unchanged. Unimproved patients showed no change in postoperative resting ventilation when compared with the preoperative observations.

(5) Inspection of the preoperative findings, both clinical and physiologic, obtained in patients who survived operation, suggests that well compensated patients with mitral stenosis as the predominating clinical feature, normal sinus rhythm and pulmonary hypertension are likely to benefit from mitral commissurotomy. In patients with atrial fibrillation, marked pulmonary hypertension and congestive heart failure, operation is hazardous and the likelihood of benefit is small. On the other hand, patients with atrial fibrillation, good cardiac compensation and only moderate pulmonary hypertension may benefit greatly from mitral commissurotomy. However, selection of candidates for operation from patients in this category is difficult because of the absence of clear-cut preoperative clinical and physiologic difference between improved and unimproved patients studied thus far. A larger series is obviously indicated and further study is in progress.

Summario in Interlingua

(1) Dece-octo patientes, seligite pro commissurotomia mitral super le base de considerabile anormalitates hemodynamic e incapacitate physic, esseva studiate ante e post le intervention chirurgic.

(2) Dece-tres patientes del serie exhibiva post le operation objective e etiam subjective signos clinic de meliorate functiones cardiocirculatori. In tres casos meliorationes subjective esseva asserite ben que sin supporto de objective datos clinic, e duo patientes remaneva nettemente sin melioration.

(3) Quando un inequivocamente objective melioration clinic esseva observate post le commissurotomia mitral, studios physiologic de 13 meliorate patientes demonstrava un augmento del rendimento cardiac e un reduction del pression median del arterias pulmonar in 6 casos, un reduction del pression median del arterias pulmonar sin marcate alteration del rendimento cardiac in 5 casos, e un augmento del rendimento cardiac sin notabile alteration del pression median del arterias pulmonar in 2 casos.

(4) Ante le operation, ventilation in reposo esseva elevate in omne patientes. Post le operation, einque meliorate patientes monstrava significative reductiones del ventilation in reposo; le alteres esseva plus o minus inalterate. Le non-meliorate patientes monstrava nulle alteration postoperative del ventilation in reposo, comparate con le correspondente observationes ante le operation.

(5) Le examine del constatationes pre-operative, tanto clinic como etiam physiologic, que esseva obtenite in patientes qui superviveva al operation, supporta le these que ben-compensate patientes con stenosis mitral como predominante tracto clinic e con normal rhythmos sinusal hypertension pulmonar va probabilemente profitar de commissurotomia mitral. In patientes con fibrillation atrial, marcate hypertension pulmonar, e congestive disfallimento cardiac, le operation es hazardose e le probabilitate de profito es basse. Del altere latere, patientes con fibrillation atrial, un bon grado de compensation cardiac, e solmente moderate hypertension pulmonar pote profitar grandemente ab comissurotomia mitral. Sed le selection de candidatos pro le operation es difficile in iste categoria a causa del absentia de clar pre-operative differentias clinic e physiologic inter meliorate e non-meliorate patientes usque nunc studiate. Le investigation de un plus extense serie de casos es obviemente requirite. Un studio de iste genere es in progresso.

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Studies on the Renal Circulation and the Renal Function in Mitral Valvular Disease

III. Effect of Valvulotomy

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Renal circulation and function were studied simultaneously with pulmonary and systemic hemodynamics in 25 patients with mitral stenosis before and six weeks after valvulotomy. Postoperatively no essential change in renal circulation or function could be demonstrated whether significant relief of pulmonary hypertension had occurred or not. However, results from follow up studies made on 21 patients up to more than three years after operation showed that renal plasma flow could be increased in patients that were hemodynamically improved at the postoperative study. The effect of exercise was investigated in eight patients before and after valvulotomy. In seven the response pattern of renal circulation and function was essentially unchanged regardless of whether improvement in pulmonary pressures and cardiac output did or did not occur. In the eighth patient, the only one with elevated right atrial pressure before operation, the response to exercise improved markedly. Preoperative results obtained on seven patients who died in connection with operation showed that a fatal outcome was not necessarily related to the degree of impairment in renal circulation or function.

THE direct surgical attack on narrowed mitral valves has established itself in the past six years.[7] The application of the cardiac catheterization technic[6] has made possible the evaluation of circulatory changes following surgical treatment. The vast majority of reports published so far are concerned with changes in clinical findings and alterations in cardiopulmonary hemodynamics.[7, 14, 15, 17]

Impairment of the renal circulation and the renal function in mitral valvular disease has been demonstrated.[1, 11, 18, 19] Recent studies have disclosed that these features roughly parallel the severity of disease and may even precede the onset of major hemodynamic alterations in the cardiopulmonary circulation.[19] The purpose of this study is to report the effects of mitral valvulotomy on the renal circulation and function and to compare these findings with observed alterations in cardiopulmonary hemodynamics.

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Material

The present study is mainly concerned with investigations performed on 25 patients before and after mitral valvulotomy. On clinical and radiologic evidence, each patient was considered to have mitral valvular disease, predominantly stenosis. Diagnosis was confirmed at operation. Patients with other complicating valvular involvement were excluded. No patient had any record of renal disease, nor any clinical signs thereof. All patients except one, case 565, had a normal right atrial pressure.

No attempt to report the clinical effects of operation was made in this study. Classification of patients was made only on the basis of alterations in cardiopulmonary hemodynamics, following operation. All patients were operated upon by Clarence Crafoord, M.D., at the Surgical Clinic of Sabbatsberg's Hospital, Stockholm, Sweden. Included also are reported results from preoperative studies on seven patients who died in connection with operation. The causes of death are shown in table 4.

The studies on the 32 patients, which are the basis of this paper were performed during the years 1951 to 1954. Studies made on some other operated patients during this period are not reported here

because renal investigations were not done, due to technical reasons.

Methods

All patients were studied in the morning, recumbent, and in the postabsorptive state. An indwelling catheter was placed in the urinary bladder. The renal clearance for para-aminohippurate (PAH) was determined after a single, intramuscular injection according to the method of Bucht.[4, 5] The renal clearance for inulin was determined after a single, intravenous injection. In patients 630/766, 666/726 and 685/755 para-aminohippurate and inulin were administered intravenously after a priming injection with a continuous injection syringe. Clearances were determined simultaneously. Urine was collected at 10 to 15 minute intervals, the bladder being rinsed twice with distilled water. The urinary content of sodium was determined by flame photometry. Resting clearance values were obtained from the mean of two or three periods.

The pulmonary artery was catheterized according to the method of Cournand and Ranges[6] as modified by Lagerlöf and Werkö.[12, 13] An indwelling arterial needle was placed in the brachial artery. The cardiac output was determined by the direct Fick method. Blood gases were determined according to van Slyke and the air gases on a Haldane apparatus. Pressures were recorded by the Tybjærg-Hansen and Warburg electric capacitance manometer.[16]

Resting observations on pressures and flow were obtained after the patient had been at complete rest for at least half an hour. The details of technics used were reported earlier.[19]

The response to graded exercise was investigated in some patients by studies on pressures, flow, renal clearances and urinary sodium excretion. Measurements were made during 10 to 15 minutes of exercise.[9, 10, 19] Work was continued during all these determinations.

As a rule patients were reinvestigated in the same manner after a period of six weeks following the operation. In 21 patients, renal clearances were determined again at different time intervals, up to more than three years after operation.

Results

The criterion of hemodynamic improvement was a decrease after operation of the pulmonary arterial pressure-cardiac index quotient by at least one-third. Accordingly, 16 patients out of 25 were considered to have been improved. Table 1 shows the results of studies made on improved patients.

The pulmonary arterial and capillary venous pressure decreased markedly on the average and the cardiac output rose. The pulmonary capillary venous pressure fell to within normal limits in nine patients, while in only one did this pressure exceed a level of 16 mm. Hg after operation. In contrast to this the pulmonary arterial pressure returned to normal limits in five patients only; in two of the remaining the pressure was still as high as 38 and 52 mm. Hg, respectively.

In the one patient, 565/606, with elevated right atrial pressure before operation, a normal value was recorded after. There was on an average no significant change in pulse rate or in brachial arterial pressure.

The renal clearance of para-aminohippurate (PAH) was mainly unchanged after operation. A substantial increase was, however, observed in three patients, 565/606, 601/632 and 685/755. In one patient, case 666/726, there was a decrease. The para-aminohippurate clearance was over 400 ml per minute in six patients before and in seven after operation.

Greater differences were observed in the renal clearance of inulin. There was a substantial increase in five patients, Cases 436/488, 554/592, 565/606, 601/632 and 685/755. On the average the inulin clearance increased by 15 per cent.

Table 2 lists results in nine patients who were considered hemodynamically unimproved according to the criterion mentioned above. There was thus on the average no change in pulmonary pressures or flow in these nine patients.

The mean preoperative value for para-aminohippurate clearance was of the same order as in the former category. A marked increase was recorded in patients 424/479, 630/766 and 695/728. A considerable fall was noted in patients 392/418 and 403/499. The para-aminohippurate clearance was over 400 ml. per minute in three patients before and in four after operation.

The renal clearance of inulin was on an average of the same order in the patients listed in table 1 as in this set of patients. In the latter group, a marked increase was observed in patients 388/452, 424/479, 630/766 and 695/728. There was a considerable fall in patient 392/418, but the postoperative value was still within normal limits.

TABLE 1.—*Clinical Data, Arterial Oxygen Saturation, Mean Pulmonary and Systemic Blood Pressures, Cardiac Index and Renal Clearance of Inulin and Para-aminohippurate in Sixteen Patients with Mitral Stenosis*

Case No.	Sex	Age	Heart Vol. ml./M.² BSA	Rhythm	Art. O_2 Sat. Per Cent	Pulse Rate	Mean Pressure mm Hg				A-V O_2 Diff. ml./L.	Card. Ind. L./min./ M.² BSA	Clearance ml./min./1.73 M.² BSA	
							PCV	PA	RA	BA			Inulin	PAH
292	F	31	680	S	91.7	76	24	47	3	80	57	2.7	105	311
321			680	S	93.7	78	14	24	3	97	46	3.0	109	325
315	F	39	575	S	95.5	100	22	28	1	98	52	3.4	113	543
340			500	S	94.6	98	21	29	2	115	38	6.3	127	611
316	M	38	620	S	90.7	78	25	41	3	108	51	2.8	68	232
350			640	S	93.6	68	11	23	1	115	44	3.6	70	181
334	F	39	480	S	92.9	72	21	32	1	104	50	2.5	127	473
490			530	S	87.5	82	16	23	4	99	28	4.9	153	445
337	F	44	470	S	94.0	76	19	21	4	100	46	2.8	129	479
369			470	S	87.2	92	10	17	0	98	42	3.7	134	488
397	F	43	520	AF	91.5	86	21	25	2	74	43	3.2	98	361
456			520	S	87.7	76	10	19	1	70	40	3.9	114	420
408	F	41	400	S	86.4	120	40	109	3	84	56	2.3	95	257
481			500	S	90.0	125	15	52	−1	93	32	4.2	97	325
436	F	33	510	S	93.7	107	22	42	−1	85	36	4.2	116	432
488			510	S	96.2	112	14	28	1	89	32	4.4	150	454
438	M	23	410	S	86.4	66	27	31	0	90	42	3.6	72	267
520			530	S	90.9	66	11	19	1	75	32	3.9	81	321
462	F	43	430	S	92.9	120	23	35	0	100	37	3.8	134	410
497			360	S	92.3	118	13	28	—	89	36	4.9	145	459
464	F	40	480	AF	87.9	95	23	47	4	100	47	2.4	137	341
496			480	S	95.4	86	8	30	−2	62	39	3.2	117	280
554	F	42	465	S	93.1	71	21	23	2	69	52	3.3	102	301
592			465	S	—	73	5	10	3	77	50	2.6	135	319
565	F	44	600	S	94.2	62	32	74	9	75	66	2.1	77	116
606			600	S	96.1	71	10	38	3	78	41	3.1	120	284
601	F	44	500	S	90.5	115	26	55	0	89	45	4.2	91	299
632			500	S	95.0	102	11	26	1	83	35	4.7	126	384
666	F	47	650	S	93.3	74	14	25	1	111	44	2.6	87	383
726			505	S	93.6	83	5	19	−1	128	30	4.4	72	291
685	M	26	950	S	88.8	81	15	35	−2	75	50	2.6	95	408
755			950	S	90.7	80	15	27	3	—	37	4.7	137	546
n.....		16	16		15	16	16	16	15	15	16	16	16	16
Mean (before op.).....		38.6	546		91.4	87.4	23.4	41.9	2.0	91.1	48.4	3.0	102.9	350.8
Diff. (pre-postop.)....			0		0.9	0.7	−11.6	−16.1	−0.7	0.1	−10.8	1.1	15.0	32.4

Investigation was made before valvulotomy (upper case number) and six weeks after (lower case number). This set of patients was considered hemodynamically improved on the grounds that the quotient pulmonary arterial pressure/cardiac index had decreased by at least one third after operation.

PCV = pulmonary capillary venous pressure; PA = pulmonary arterial pressure; RA = right atrial pressure; BA = Brachial arterial pressure; A-V O_2 diff. = arteriovenous oxygen difference; PAH = para-aminohippurate; n = number of cases; BSA = body surface area.

Differences between pre- and postoperative values for renal clearances and hemodynamic data were compared. No correlation was found. This was true for both sets of patients and for the total material.

The effects of a slight, graded, exercise test was studied in eight patients, four from each group. Figure 1 illustrates the results obtained in two patients. In patient 438/520 (table 1) the response to exercise after operation showed a marked improvement in the pulmonary hypertension present before operation. The

TABLE 2.—*Clinical Data, Arterial Oxygen Saturation, Mean Pulmonary and Systemic Blood Pressures, Cardiac Index and Renal Clearance of Inulin and Para-aminohippurate in Nine Patients with Mitral Stenosis*

Case No.	Sex	Age	Heart Vol. ml./M.² BSA	Rhythm	Art. O_2 Sat. %	Pulse Rate	Mean Pressure mm. Hg				A-V O_2 Diff. ml./L.	Card. Ind. L./min./M.² BSA	Clearance ml./min./1.73 M² BSA	
							PCV	PA	RA	BA			Inulin	PAH
354	F	45	390	S	92.6	65	16	19	3	94	40	2.6	102	400
376			480	S	92.0	67	17	27	—	103	44	2.8	95	373
360	F	40	630	AF	91.0	80	29	39	1	155	49	2.7	105	287
379			630	AF	90.0	84	24	34	5	—	58	2.4	105	290
380	M	46	590	AF	95.9	66	12	20	0	108	54	2.1	76	260
415			430	AF	96.0	76	13	23	2	—	52	2.3	77	209
388	F	30	560	S	93.8	82	25	36	0	88	32	4.9	89	394
452			560	S	82.1	75	14	28	4	81	28	5.1	133	403
392	F	26	410	S	93.0	120	14	28	1	92	29	5.1	198	646
418			410	S	90.5	108	13	20	1	95	41	4.3	132	456
403	M	45	420	S	92.5	63	28	32	2	90	47	2.9	111	412
499			420	S	92.4	77	23	38	2	75	37	4.6	87	227
424	M	34	500	S	92.6	71	18	22	0	102	50	3.4	84	349
479			500	S	97.1	79	14	15	3	95	63	2.1	125	552
630	M	38	500	S	94.3	59	18	27	0	74	52	2.6	50	197
766			510	S	—	75	10	27	0	76	50	2.8	87	380
695	F	39	690	AF	91.7	70	16	22	5	61	49	3.9	109	324
728			580	AF	92.0	79	10	18	6	79	49	2.5	140	426
n.....		9	9		8	9	9	9	8	7	9	9	9	9
Mean (before op.).....		38.1	521		92.9	75.1	19.6	26.7	1.1	85.9	44.7	3.4	102.7	363.2
Diff. (pre-postop.)....			−19		−1.4	4.9	−4.3	−1.1	1.8	0.4	2.2	−0.2	6.3	5.2

Investigation was made before valvulotomy (upper case number) and six weeks after (lower case number). This set of patients was considered hemodynamically unimproved on the grounds that the quotient pulmonary arterial pressure/cardiac index did not decrease by one-third after operation.

PCV = pulmonary capillary venous pressure; PA = pulmonary arterial pressure; RA = right atrial pressure; BA = brachial arterial pressure; A-V O_2 diff. = arteriovenous oxygen difference; PAH = para-aminohippurate; n = number of cases; BSA = body surface area.

cardiac output was higher after operation. There was no change observed in either right atrial or brachial arterial pressures. The renal clearance of both para-aminohippurate and inulin showed the same response to exercise, both before and after operation. A moderate fall in sodium excretion was noted both in the pre- and the postoperative study.

Essentially the same response to exercise was observed in seven out of these eight patients. The results in patient 565/606 (table 1) show a different pattern. This was the only patient with elevated right atrial pressure present before operation. Following surgery pulmonary pressures fell and cardiac output rose. Renal clearances increased markedly and the response to exercise became normal. There was no decrease in sodium excretion on the postoperative exercise test. The pathologically elevated right atrial pressure decreased to a normal level and stayed normal even on effort.

Table 3 (*A* and *B*) contains the results of all clearance determinations made before, immediately after and up to three years after the operation. The material is divided into two groups according to the same criterion already used. Two patients were reinvestigated when they were admitted to the hospital because of complicating disease (cases 315/340 and 334/490). In these the clearance values were markedly lower at the time of reinvestigation than before.

Some patients after successful operation had a progressive increase in renal clearances over

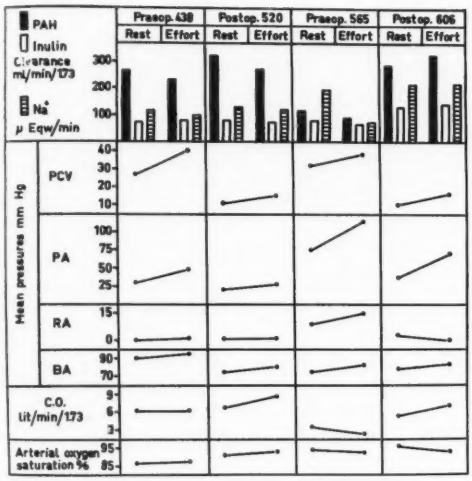

FIG. 1. Response to exercise of the renal clearance of para-amino-hippurate and inulin, urinary sodium excretion, mean pressures in the pulmonary and systemic circulation, cardiac output and arterial oxygen saturation in two patients with mitral stenosis before and after valvulotomy (see text).

PAH = para-aminohippurate; Na^+ = urinary sodium excretion; PCV = pulmonary capillary venous pressure; PA = pulmonary arterial pressure; RA = right auricular pressure; BA = brachial arterial pressure; C.O. = cardiac output.

the years until normal values were reached (cases 601/632 and 462/497 table 3a). Others also showed increased values after the successful valvulotomy although not to the same extent (cases 316/350, 408/481, 438/520, table 3*A*). This was also observed in one patient, who was classified as hemodynamically unimproved at the first postoperative study (case 630/766, table 3*B*).

Of the patients in table 3*A* only one (case 337/369) had lower clearance at follow up than before operation. She had atrial fibrillation at the time of study. The clearances did not improve following reconversion to sinus rhythm. In another patient (case 464/496, table 3*A*), also fibrillating at the time of the third study, conversion to sinus rhythm was accompanied by a marked increase in renal clearances.

All other patients in the improved group had virtually unaltered clearances during the follow up period. In the other group most patients had unaltered or decreasing clearances (especially the para-aminohippurate clearance) during the follow up period.

Table 4 shows the preoperative studies and autopsy findings in those seven patients who died immediately after operation. Average figures show that the severity of disease was generally more marked as compared with the severity in those who lived after operation, as judged from pulmonary pressures and cardiac output. The para-aminohippurate clearance was over 400 ml. per minute in one patient only, case 567. Moderately low figures were observed in the remaining studies, except for patients 569 and 576, where a markedly low value was recorded. In the latter patients the

TABLE 3*A*.—*Renal Clearances of Inulin and Para-aminohippurate (PAH) in Fourteen Patients with Mitral Stenosis*

Case No.	Clearance ml./min./1.73 M.² BSA							
	Inulin				PAH			
	I	II	III	IV	I	II	III	IV
292/321	105	109	103	92	311	325	326	300
315/340	113	127	113	—	543	611	382	—
316/350	68	70	99	99	232	181	272	356
334/490	127	153	129	—	473	445	347	—
337/369x	129	134	113	—	479	488	382	—
			97				342	
397/456	98	114	104	—	361	420	360	—
408/481	95	97	120	—	257	325	387	—
436/488	116	150	129	—	432	454	445	—
438/520	72	81	83	—	267	321	333	—
462/497	134	145	163	—	410	459	597	—
464/496x	137	117	108	—	341	280	322	—
			141				415	
554/592	102	135	108	—	301	319	315	—
601/632	91	126	112	—	299	384	625	—
666/726	87	72	103	—	383	291	415	—
Mean...	102.8	112.5	112.8	95.5	339.4	353.9	400.5	328.0

All patients were considered hemodynamically improved by valvulotomy (for criterion see table 1 or text). Determinations were made before valvulotomy (I), approximately six weeks after operation (II) and one and one half to two years after the postoperative study (III). In two patients, determinations were repeated again after three years (IV) and in two (x), after conversion of atrial fibrillation to normal sinus rhythm.

Cases 315/340 and 334/490 are not included in the averages as they had complicating diseases at the time of follow-up study.

TABLE 3B.—*Renal Clearances of Inulin and Para-aminohippurate (PAH) in Seven Patients with Mitral Stenosis*

Case No.	Clearance ml./min./1.73 M² BSA					
	Inulin			PAH		
	I	II	III	I	II	III
354/376	102	95	105	400	373	326
380/415	76	77	86	260	209	211
388/452	89	133	125	394	403	298
392/418	198	132	165	646	456	483
424/479	84	125	95	349	552	373
630/766	50	87	101	197	380	339
695/728	109	140	107	324	426	318
Mean.....	101.1	112.7	112.0	367.1	399.9	335.4

All patients were considered hemodynamically unimproved by valvulotomy (for criterion see table 2 or text). Determinations were made before valvulotomy (I), approximately six weeks after operation (II) and one and one half to two years after the postoperative study (III).

there were no renal emboli and the kidneys weighed 350, 260 and 400 Gm., respectively. In the remaining patients old renal infarcts were found to a various extent and the kidney weight was lower. In patient 569, who had the lowest renal clearance, the left kidney was completely destroyed and the right contained several infarcts.

DISCUSSION

In patients with mitral valvular disease varying degrees of impairment of the renal function, as measured by para-aminohippurate and inulin clearance, are present.[18, 19] The decrease in clearances and those alterations in the pulmonary or systemic circulation that are more directly caused by the heart lesion have, however, generally correlated poorly. The closest relationship has been established between elevation of pulmonary arterial pressure and

TABLE 4.—*Clinical Data, Arterial Oxygen Saturation, Mean Pulmonary and Systemic Blood Pressures, Cardiac Index, Renal Clearance of Inulin and Para-aminohippurate and Autopsy Findings in Seven Patients with Mitral Stenosis Who Died Immediately after Operation*

Case No.	Sex	Age	Heart Vol. ml./ M.² BSA	Rhythm	Art. O_2 Sat. Per Cent	Pulse Rate	Mean Pressure mm. Hg				A-V O_2 Diff. ml./L.	Card. Ind. L./ min./ M.² BSA	Clearance ml./min./1.73 M.² BSA		Cause of Death	Kidney Weight Gm.	Remarks
							PCV	PA	RA	BA			Inulin	PAH			
358	F	42	590	S	87.5	90	22	59	2	112	47	3.3	82	313	Arterial embolism	195	Renal infarcts
367	F	46	630	S	76.6	109	25	88	2	110	60	2.5	112	285	Arterial embolism	200	Renal infarcts
402	M	45	720	AF	94.5	80	27	47	1	87	62	2.1	132	369	Circulatory failure	350	—
463	M	40	760	AF	89.2	95	19	44	1	119	64	2.1	104	301	Circulatory failure	250	Renal infarcts
567	F	32	500	S	87.8	71	19	26	0	73	36	4.1	115	432	Virus pneumonia	260	—
569	M	40	450	AF	92.1	65	29	46	2	80	72	1.9	41	119	Arterial embolism	180	Extensive renal infarctions
576	M	40	1400	AF	85.0	97	32	89	14	124	73	1.7	66	153	Circulatory failure	400	—
n....		7	7		7	7	7	7	7	7	7	7	7	7			
Mean		40.7	721		87.5	86.7	24.7	57.0	3.1	100.7	59.1	2.5	93.1	281.7			

PVC = pulmonary capillary venous pressure; PA = pulmonary arterial pressure; RA = right atrial pressure; BA = brachial arterial pressure; A-V O_2 diff. = arteriovenous oxygen difference; PAH = para-aminohippurate; n = number of cases; BSA = body surface area.

inulin clearance was also very low. In the other studies the inulin clearance was over 100 in all except one patient, case 358.

In three patients, cases 402, 567 and 576, decrease in renal plasma flow.[18, 19] The present study was undertaken to find out whether the decrease in pulmonary arterial pressure and increase in cardiac output when caused by surgi-

cal therapy would influence the renal plasma flow.

The results have shown that the decreased renal plasma flow in mitral stenosis may rise markedly after successful valvulotomy and that further increase may occur over a period of some years. This was not the rule in all improved patients, as in many of them only slight or no improvement in the renal circulation could be demonstrated. In three patients, also classified as improved at the immediate postoperative study, renal clearances had decreased at the time of follow up. Two of these patients had had repeated attacks of carditis and the third was studied during and after an attack of atrial fibrillation. It seems probable that these complications may have influenced both the general and renal circulation in an adverse manner. In the absence of such complications successful valvulotomy was always followed by unaltered or improved renal circulation at the late follow up.

On the contrary, most of the patients who were classified as unimproved at the postoperative catheterization either demonstrated unaltered or further diminished renal plasma flow at the follow up study.

The criteria for hemodynamic improvement used in this paper have been made rather advanced. It is furthermore possible that the course of the disease in each patient during the following years may modify the immediate response to operation, in some patients causing further improvement, in others further decrease of function. Several patients in the hemodynamically unimproved group showed a moderate to marked clinical improvement at the follow up and some patients in the improved group had experienced increasing symptoms at this time. It is of interest to note that, notwithstanding these irregularities in the patient material, the improved group as a whole had much better renal circulation in the follow up studies as compared with the unimproved group.

The first postoperative study was done about six weeks after operation when the patients were still hospitalized. In some of the improved patients the increase in renal plasma flow occurred gradually as they resumed living an active life, as a consequence of successful operation. This is in accordance with observations on the exercise tolerance after valvulotomy that have shown that there may be a gradual improvement up to about nine months after operation.[3] This finding is similar to the observation that the decreased renal plasma flow occurring in anemia may remain low as long as six months after the correction of anemia and then increase to normal.[2]

The renal plasma flow may be decreased in patients with mitral valvular disease even if the pulmonary circulation is normal at rest.[19] In the present series surgical treatment caused marked relief of pulmonary hypertension in several patients. Even in those who were markedly improved the pulmonary vascular pressures only partly returned to normal level. It was not likely that pathologically low renal clearances present before operation should reach normal levels after operation although some improvement could be expected. The immediate postoperative values for the improved group, however, were lower than in nonoperated patients with comparable pulmonary circulation.[18, 19] At the follow up study the group as a whole had higher clearance values, which more closely corresponded to what was expected from studies on nonoperated patients.[18, 19]

The unaltered level of renal clearance in many patients after operation once again brings out the fact that surgical intervention does not cure patients with mitral stenosis but only improves the circulation to a certain degree.[7] This is substantiated by the results obtained on the exercise test. This fact is of importance when indications for surgical treatment are discussed. On the other hand the presence of even markedly decreased renal clearances does not constitute any contraindication to operation, which is amply demonstrated in patient 565/606 (table 1) with markedly elevated right atrial pressure before operation. Afterwards the pulmonary pressures were markedly decreased, and also the right atrial pressure. The latter did not increase during exercise after operation in contrast to before operation. The renal plasma flow had risen, although not to a normal level, and, the decrease in renal plasma flow and sodium excretion during exercise was insignificant. Thus

renal function reacted to the burden of exercise almost in a normal fashion after surgery, in contrast to the marked pathologic reaction before.

The remarkably stable level of renal plasma flow during many years in some patients may indicate the presence of pathologic lesions in the kidneys, prohibiting any improvement of its function. Patient 403/479 (table 2) had multiple emboli after operation, including mesenteric and probably renal. This patient had very marked decrease in para-aminohippurate clearance. The postmortem studies allow some comments on this matter. Patient 569, who died at operation, had extensive renal infarcts. He had the lowest renal plasma flow of all of our patients. On the other hand, patient 576 (table 4), who also had a similarly low renal plasma flow, had large congested kidneys at autopsy without any emboli. It has been shown that the renal plasma flow in patients with mitral stenosis may increase to normal values following the administration of Apresoline,[20] during a rapid infusion of isotonic glucose solution[8] or during fever.[21] One of the patients in the present series, who was improved after surgery, had a lower renal plasma flow and filtration rate at the postoperative study than before. When the patient was studied during the rapid infusion of isotonic glucose solution, both renal plasma flow and filtration rate increased to the same, normal value.[8] Similar findings have been recorded in other patients. Even though the renal plasma flow thus is low, the patient still has the ability to increase the renal function. This reserve capacity seems to be unaltered by the operative procedure.

The preoperative studies on those patients who did not survive operation show that renal clearances are not necessarily low in patients where the operative outcome is fatal.

Summary

(1) Pressures in the pulmonary and systemic circulation, cardiac output and renal clearances of para-aminohippurate and inulin were determined simultaneously in 25 patients with mitral valvular disease. Patients were reinvestigated in the same manner about six weeks after valvulotomy. In eight patients the effect of exercise was studied pre- and postoperatively.

(2) The renal clearance of para-aminohippurate was essentially unaltered after operation whether alleviation of pulmonary hypertension had occurred or not.

(3) Results from follow-up studies made on 21 patients up to more than three years after operation showed that definite increase in renal plasma flow occurred in patients with improved pulmonary circulation.

(4) One patient only had pathologically elevated right atrial pressure before operation. After operation, this pressure became normal, both at rest and during exercise, and a marked improvement of both pulmonary circulation and renal function was observed.

(5) Preoperative results on seven patients who died immediately after operation showed that a fatal outcome was not related to the degree of impairment in renal function.

Summario in Interlingua

Circulation e functiones renal esseva studiate simultaneemente con le hemodynamica pulmonar e systemic in 25 patientes de stenosis mitral ante e 6 septimanas post valvulotomia. Post le operation nulle alteration essential del circulation o function renal esseva demonstrabile, si o non un alleviamento significative del hypertension pulmonar habeva occurrite. Tamen, resultatos de studios posttractamental executate pro 21 patientes durante periodos de usque a plus que tres annos post le operation monstrava que le fluxo renal de plasma esseva augmentabile in patientes qui se monstrava hemodynamicamente meliorate al tempore del studio postoperative. Le effecto de exercitio esseva investigate in octo patientes ante e post le valvulotomia. In septe casos le responsas del circulation e function renal esseva plus o minus inalterate, sin reguardo a si o non un melioration del pression pulmonar e del rendimento cardiac habeva occurrite. In le octave patiente, le sol con elevate pression dexteroauricular ante le operation, le responsa a exercitio se meliorava marcatemente. Le resultatos de observationes pre-operative in septe patientes qui moriva in connexion con le operation monstrava que un

termination mortal non esseva necessarimente connectite con le grado de disrangiamento in le circulation e function renal.

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Livedo Reticularis with Ulcerations

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Idiopathic livedo reticularis may be associated with ulcerations of the lower extremities beginning primarily during the warmer or summer months, as well as the more usual occurrence of winter ulcerations. Summer ulceration apparently is a new and rare entity which has many clinical and histopathologic features similar to winter ulcerations. Hypertension, Raynaud's phenomena, acrocyanosis and thrombosis of digital arteries were noted only in patients with winter ulcerations, while edema of the legs and feet was a more prominent feature in patients with summer ulcerations. Medical treatment, including rest in bed, elastic supportive bandages and a trial of hexamethonium (bistrium bromide) injections, seemed to be the treatment of choice. Lumbar sympathectomy did not seem to be of great permanent value.

ALTHOUGH idiopathic livedo reticularis* may occasionally be associated with ulcerations, a thorough clinical and histopathologic study of this condition has seldom been reported. It has been assumed that the effect of cold on the blood vessels of the skin accounted for the predominance of the symptoms and the occurrence of the ulcerations during the winter months. However, in reviewing the records of more than 400 patients seen in the Mayo Clinic in the past 10 years with a diagnosis of livedo reticularis and pernio,† we have been able to define a group of patients with a new entity in that idiopathic livedo reticularis is associated with ulcers starting only or primarily during the warm months of the year, especially during the summer.[1]

The first part of this report will briefly summarize some of the medical literature concerning livedo reticularis, and the second part will contain the data on winter and summer ulcerations in livedo reticularis.

1. Review of the Medical Literature Concerning Livedo Reticularis

Definitions

Livedo reticularis is a condition of the skin characterized by a reddish blue, mottled, reticular or blotchy discoloration. It persists with a variation of degree regardless of the skin temperature, and has also been described as a marbling or a fish-net discoloration. Synonyms in the medical literature for this condition have been "generalized telangiectasia," "livedo racemosa," "livedo annularis" and "asphyxia reticularis."

"Cutis marmorata" is a term generally used for a transient reticular discoloration which appears on exposure to cold, as in livedo reticularis, but is not permanent and disappears with warmth. The term has been used interchangeably with "livedo reticularis" in the medical literature.

The word "livedo" is derived from the Latin word, "liveo," meaning to be black, blue or livid. The term was used by Hebra in 1868.[2]

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* Unless otherwise designated, the term "livedo reticularis," when mentioned in this report, applies to idiopathic livedo reticularis, not to symptomatic livedo reticularis as a result of such diseases as periarteritis nodosa or which has been described with tuberculosis or syphilis.

† Pernio, when mentioned in this report, refers to the disease known as "perniones" (erythema pernio, chronic chilblains, frostbeulen and frostbites) resulting from exposure to cold. It is not used in the sense of "lupus pernio" (Besnier), which is a manifestation of sarcoid, or "lupus pernio" (chilblain lupus, Hutchinson), which represents the cutaneous manifestations of disseminated lupus erythematosus.

The local coloration, he believed, was the result of idiopathic passive hyperemia and he proposed the term "livor cutis, livedo (Blauung)." Kaposi[3] stated that the discoloration was due to an excessive amount of blood in the most superficial layer of the corium and that it was due solely to "the injection of the finest vessels, the capillaries and the finest arteries and veins." Unna,[4] Ebert,[5] Lewis[6] and Williams and Goodman[7] discussed the pathologic physiology of livedo reticularis. Rothman[8] has presented a review of the recent concepts of vascular anatomy and physiology of the skin. He implied that cutis marmorata is due to a developmental anomaly of the cutaneous vascular system and is not connected with any particular disease, but that livedo reticularis, in contrast, is a consequence of arteriolar disease. The reticular areas seemed to be more vulnerable to inflammatory stimuli than the pale areas, possibly because there were more open vessels in the reticulum.

To summarize, a possible concept of the physiopathologic mechanism of livedo reticularis could be as follows: Blood supply to the skin is from central arterioles which pierce the skin from below and the central zone capillary arborizations have a slightly greater tone and faster blood flow than in peripheral capillaries. Then, either through organic changes or through vasospasm of arteries or arterioles of the skin, capillary atony and slowing of blood in peripheral capillaries is further increased, which results in a livedo reticularis pattern in annular rings about central paler areas. Cold causes increased vasoconstriction of arteries and arterioles, resulting in an intensification of the livedo. Peripheral capillaries, if temporarily atonic and dilated, would result in a transient cutis marmorata or, if permanently dilated, would result in a permanent discoloration. On elevation of the affected part, the livedo might decrease if the venules draining the capillaries were not obstructed and could dilate and drain the stagnant blood from the capillaries. Warmth and sympathectomy could reduce the vasospasm of the arteries and arterioles and also result in less discoloration.

Clinical Types of Livedo

Livedo reticularis is best classified after Williams and Goodman[7] with some modifications.

(1) *Cutis Marmorata.* This is a transitory mottling with exposure to cold. There is probably no pathologic alteration in the peripheral circulation, but it is only the result of a vasomotor phenomenon. It is frequent in infants and may disappear as they grow older.

Aldao[9] reported that cutis marmorata of 24 to 48 hours' duration may be the only cutaneous manifestation, or one of the cutaneous manifestations, of compressed-air illness. The cause was considered to be an obstruction of the vessels of the skin with air emboli resulting in ischemic areas and also areas of passive congestion.

(2) *Idiopathic Livedo Reticularis.* This is manifested by a relatively permanent mottling which persists in a variation of degree, amount and arrangement regardless of temperature changes. This group includes cases in which no definite local or systemic disease is discovered as an explanation for the livedo. Williams and Goodman[7] expressed the belief that this is an anomaly of the blood vessels, possibly congenital. There may be minimal or no organic changes in the vessels except increased number and dilatation of the capillaries in the livid areas, although more severe organic changes have been noted in the blood vessels. Such cases have been reported by several authors.[7, 10-12] Brain[13] has reported data on two children, 9 weeks and 13 years of age respectively, who have had "naevus vascularis reticularis" present since birth.

(3) *Symptomatic Livedo Reticularis.* This group could be divided into three subdivisions.

A. Questionable Factors in Livedo Reticularis

The literature of livedo reticularis contains many reports of livedo reticularis in patients with various diseases, such as in children with rickets, mongolism, various endocrine dysfunctions, such as hyperthyroidism, hypothyroidism, pituitary disorders, such as Cushing's disease, malnutrition, varicose veins and

other vascular diseases such as arteriosclerosis, infectious diseases (typhus) and toxic conditions (arsphenamine intoxication), congenital vascular defects and ectodermal abnormalities, cirrhosis of the liver and other visceral diseases. Nerve injuries may result in livedo reticularis and a patient believed to have perniones and livedo of a poliomyelitic limb was presented at a dermatologic meeting by Senear.[14] Local livedo racemosa only about the site of an intramuscular injection of bismuth has been noted.[15] It was believed to be due to an unintentional intra-arterial injection of bismuth with subsequent embolus and occlusion of smaller vessels in the vicinity resulting in a livedo reticularis pattern.

The influence of some of these diseases on the pattern of livedo reticularis is unknown; perhaps in some of these conditions the livedo reticularis and the disease are coincidental.

Lutz and Picard[16] described a patient who had a livid eruption, clinically similar to livedo racemosa, which was worse in the winter and better during the summer, but there were areas of cutaneous atrophy which suggested anetoderma. There were no ulcerations.

B. Probable Factors in Livedo Reticularis

(1) Hypertension has been noted to occur in 30 per cent of a group of patients with livedo reticularis on whom data have been reported by Barker, Hines and Craig,[11] and there have been several isolated reports of hypertension in patients with livedo.[5, 12] It is interesting to note that arteriolar spasm is a feature in patients with hypertension and also is a major factor in the etiology of livedo reticularis.

(2) Nervousness and emotional instability were noted in about 50 per cent of patients in one series of livedo reticularis and arsenic or lead poisoning was considered a possible etiologic factor in several patients reported by the same investigators.[11]

C. Purported Causes of Livedo Reticularis

The term "inflammatory livedo" might be applied to this group, since a specific histologic picture may be found.

(1) Tuberculosis. Adamson[17] in 1916 reported data on a group of girls from 11 to 15 years of age with "chilblain circulation," generalized livedo annularis, nodules of the legs and lymphadenopathy; several had enlargement of the spleen. In two of his cases the Wassermann reaction was positive. He believed these cases to have manifestations of tuberculosis and erythema induratum with a livedolike distribution. Other scattered cases in the medical literature in which tuberculosis was considered an etiologic factor were found by Ebert[5] and Becker.[12]

An evaluation of the cases cited in the previous paragraph reveals that the evidence for tuberculosis, especially active tuberculosis, is meager. Histologic examination of a cutaneous specimen for biopsy from one of Adamson's patients was not diagnostic, and ulceration of the lower extremities cannot be assumed to be of tuberculous origin because of the clinical appearance. Although some patients with pulmonary or other systemic types of tuberculosis may have livedo reticularis and ulcerations which suggest erythema induratum, a tuberculous histopathologic picture or cultural and animal inoculation studies which reveal the organism are necessary before the ulceration can be assumed to be erythema induratum, since ulceration could be the result merely of the livedo reticularis.

(2) Syphilis. Ehrmann[18] in 1907 reported data on nine patients who had "livedo racemosa syphilitica." He believed that in patients with cutis marmorata a large macular syphilid could develop after Treponema pallidum settled in an area of sluggish capillary circulation. The discoloration was described as raised without ulceration and assumed a treelike distribution with branching. Histopathologic studies in two cases revealed constriction and some obliteration of dermal and subcutaneous arteries without any venous changes.

Since the initial reports by Ehrmann on livedo reticularis due to syphilis, the evidence for syphilis being a significant factor in the etiology of livedo has been scant and the presence of a positive serologic reaction for syphilis or a history of a luetic infection is not sufficient to enable one to conclude that a patient with livedo has "livedo racemosa syphilitica."

(3) Some cases of periarteritis nodosa have been shown by Ketron and Bernstein[19] to cause livedo reticularis and ulceration, especially in the lower extremities. Histopathologic studies revealed thrombosis with or without inflammation of vessels and occasional necrosis of small vessel walls, but larger and deeper subcutaneous vessels showed more classic changes.

Ruiter[20, 21] has reported on a group of patients having a basically similar clinical and histopathologic picture of a hematogenous, allergic, disseminated eruption ("allergic cutaneous vasculitis"). He included periarteritis nodosa which involved the medium-sized vessels of the cutaneous-subcutaneous border and distinguished it from "arteriolitis allergica," which has a similar histopathologic involvement of the smaller vessels of the corium with insignificant or no involvement of the larger arteries. Such features as superficial hemorrhage and necrosis, urticarial lesions and telangiectasia were often manifestations of allergic arteriolitis. Although livedo reticularis was not described, the clinical and histologic features of telangiectasia in allergic arteriolitis might be considered as analogues to the livedo in typical periarteritis nodosa.

Gougerot and Duperrat[22] have expressed the belief that the condition described by Ruiter[20, 21] is similar to "the nodular dermal allergides of Gougerot."

Histopathology

The histopathology of the skin from areas of lividness in cases with nonulcerative idiopathic livedo reticularis has shown a varying type and degree of changes such as dilatation and increase in number of capillaries in the upper corium, endarteritis and endophlebitis of the smaller vessels, at times with occlusion, periarteritis and periphlebitis and occasionally thickening of the walls of arterioles in the dermis and subcutaneous tissue.[5, 10, 12] Mogensen[23] reported the case of a man 48 years of age who clinically had a generalized livedo reticularis without ulceration of 20 years' duration. Histopathologic studies from an area of livedo revealed an inflammatory infiltrate of lymphocytes and plasma cells and a moderate increase of mast cells, but not as great as usually occurs in urticaria pigmentosa. The condition resembled in some respects telangiectasia macularis eruptiva (urticaria pigmentosa) and a connection with that disease was supposed.

The histopathologic changes in idiopathic livedo reticularis with ulceration have been recorded by several authors.[5, 11, 24] Ebert[5] described the case of a woman 33 years of age with ulcers of the legs for seven years, which started as subcutaneous nodules, most frequent and recurring during the summer. Persistent livedo reticularis had been present for four years. Histologic examination of a cutaneous specimen for biopsy from a nonulcerative livid area on a buttock revealed in the upper corium a perivascular round cell infiltrate with dilatation of the small vessels and lymphatics and thrombosis of veins draining the sweat glands. At the junction of the cutis and subcutis there was perivascular infiltration of a large artery and vein and proliferative changes in the walls of both vessels with thrombosis of the vein. Microscopic examination of a specimen for biopsy from a recently ulcerated nodule of the external malleolus revealed infiltration in the corium extending into the subcutaneous fat and occurring especially about vessels, sweat glands and ducts. The infiltrate consisted of leukocytes, plasma cells, lymphocytes and epithelioid cells. There were degeneration and destruction of the elastic tissue. The nutrient arteries of the subcutis and corium were hypertrophied and there was some marked proliferative change. Ebert thought that the ulceration was most probably tuberculoid, although there was no clinical or laboratory evidence of tuberculosis. This case could represent a case of livedo reticularis with summer ulceration.

Barker and Baker[24] reported extensive histologic studies of a man, aged 34 years, with livedo reticularis, ulceration of a leg and thrombosis of the great toe. Microscopic examination of a specimen for biopsy from an ulcer revealed moderate fibrosis and nonspecific inflammation. No acid-fast bacilli were seen. Lumbar and cervical sympathectomies were performed but later the patient insisted on amputation of his left leg because of recurrent ulceration and pain. Pathologic examination of the removed limb revealed that the smaller blood vessels (arterioles and venules and the vasa vasorum) had proliferative and occlusive intimitis (endarteritis and endophlebitis), and thickening of the walls of arterioles also was noted but was thought to be a secondary feature. There was evidence of an ischemic neuritis with perineural and intraneural fibrosis and patchy loss of myelin sheaths. The long and short saphenous veins revealed some proliferation of the intima and some inflammation of their walls as in a venous stasis picture. The large arteries, such as the posterior tibial, showed only slight intimal proliferation without occlusion and some inflammation of their walls.

Barker, Hines and Craig[11] reported four cases with livedo reticularis and ulceration. In one case

histopathologic examination of a specimen of tissue from an ulcer revealed that the arterioles, 75 microns or less in diameter, were surrounded by lymphocytes and there was some reduction in size of the lumen associated with thickening of the vessel wall, but no definite intimal proliferation was described.

Diagnosis

The first stage in the diagnosis of livedo reticularis is made by noting a mottled, reticular, blue-red discoloration which has persisted to some degree in spite of temperature changes. Then it must be determined whether the eruption is idiopathic or symptomatic, by obtaining a thorough history, general physical examination and various laboratory examinations including chest roentgenogram, serologic tests for syphilis, sedimentation rate and in some cases a cutaneous biopsy.

If there is no ulceration, then the differential diagnosis might include acrocyanosis,[25, 26] which causes a diffuse blue color affecting the hands or occasionally the feet, which is permanent, asymptomatic, does not change with warmth and does not result in ulceration or necrosis. Histopathologic studies have revealed hypertrophy of the media of cutaneous arterioles, which could be secondary to spasm, and dilatation and new formation of cutaneous capillaries. Raynaud's disease causes intermittent symptoms classically having a triple color change of white, blue and red. It occurs in young women in 70 per cent of cases[25] and involves primarily the fingers or toes, rarely the nose and ears. There is slight, limited or no ulceration or necrosis, confined to the portions of the body involved in the color changes.

The ulceration in livedo reticularis is clinically not specific and several conditions with similar vascular changes, such as chronic pernio, hypertensive ischemic ulcer and hemolytic anemias, may result in a similar-appearing ulcer. Pernio[27] or perniones occur particularly in young women and result in localized blue-red areas without mottling, becoming redder with warmth or vasodilatation, not changing with posture, occurring only with exposure to cold and sometimes resulting in ulceration. Histopathologic examination, as reported by McGovern, Wright and Kruger,[27] revealed a pathologic picture, most characteristically revealing angiitis of the smaller cutaneous vessels, fat necrosis and some giant cells. They stated that this picture was not morphologically specific, since a number of vascular conditions involved similar histologic changes and represented a chronic irritative process, either primary or secondary, in the subepidermal tissues. The subcutaneous ulcerated nodules in extremities affected by anterior poliomyelitis or erythrocyanosis of Telford[28] probably represent perniones disease. Hypertensive ischemic ulcers[29] result occasionally in individuals who usually have had hypertension for a long time. The ulcer is indolent, small and painful, responds poorly to treatment and has an ischemic appearance. Histopathologic examination of an ulcer reveals no significant changes except in the arterioles, which reveal an increase in thickness of the arteriolar walls and decrease in the diameter of the lumen. Other changes in the arterioles include hyaline degeneration of the media, intimal proliferation and periarteritis.

Nodular vasculitis[30-35] may cause ulcerative lesions of the lower extremities and is manifested by chronic, persistent or recurrent nodules, chiefly on the legs, which are not of tuberculous origin. Ulceration occurs occasionally, especially in women past 30 years of age, although it can affect either sex at any age. Hypertension has been associated occasionally.[36]

The lesions of nodular vasculitis have the same distribution as erythema induratum but are more painful, usually of shorter duration and may clear with rest in bed and elevation of the legs. However, the clinical distinction between nodular vasculitis, erythema nodosum and the nodose type of erythema induratum is often difficult. Histopathologic examination of the lesions of nodular vasculitis reveals vasculitis with varying degree of thickening and obliterative changes in both veins and arteries, a varying degree of fibrosis of the subcutaneous tissue with collections of foreign-body giant cells and atrophy of the fat but without definite tubercle formation.

Ulceration of the lower extremities could also result from conditions such as those of factitial origin, ulceration secondary to varicose veins and venous insufficiency, arteriosclerosis obliterans, thromboangiitis obliterans and various blood dyscrasias including hemolytic anemias. But in these cases, livedo reticularis is not noted and concomitant clinical, laboratory and histopathologic studies would aid in establishing the diagnosis.

Treatment

Treatment of idiopathic livedo involves surgical and nonsurgical methods.

(1) Nonsurgical treatment includes protection from the cold, vasodilating drugs such as priscoline or hexamethonium drugs, elastic bandages for the lower extremities if edema occurs, especially with ulceration, hospitalization and rest in bed if ulceration or thrombosis occurs, and mild antiseptic dressings for the ulcerations. Typhoid vaccine has been used intravenously.[11, 24]

(2) Surgical treatment includes sympathectomy or injection of alcohol to produce sympathetic block.

Barker, Hines and Craig[11] in 1941 reported three cases in which livedo reticularis was treated with lumbar sympathectomy. Two patients with gangrene had no recurrence of gangrene after 1 and 3 years respectively and the livedo and symptoms improved. One patient reported by Barker and Baker[24] had ulceration of the legs and thrombosis of toe arteries which recurred after lumbar sympathectomy. Finally the patient insisted on amputation.

Barker, Hines and Craig expressed the belief that sympathectomy is a justifiable procedure in cases of severe livedo when no definite etiologic factor is found or when extensive gangrene is present.

Shumacker[37] reported data on a patient with livedo reticularis and coldness and numbness of the feet who improved after bilateral lumbar sympathectomy. The feet became warm and dry, there was no discomfort and only a faint dependent mottling persisted.

If the patient has tuberculosis, syphilis or periarteritis nodosa and it is believed that these diseases are factors in the etiology of the livedo, treatment should be directed toward them.

2. Data of the Present Study

A. Livedo Reticularis with Winter Ulcerations

Idiopathic livedo reticularis is not uncommonly associated with ulcerations, usually starting during the winter months. The ulcers usually occur on the normally exposed acral parts of the body, especially the lower extremities. The legs, ankles and feet are especially frequent sites of ulceration. Digital arterial occlusion of the toes occurring with livedo reticularis may result in ulceration occurring on the toes.

A brief summary of the findings in 18 patients with livedo reticularis and primarily winter ulcerations is presented in table 1 and a brief summary of the histories of two patients follows:

Report of Cases (Patients 1 and 2, Table 1)

Case 1. A white, divorced, female clerk, aged 24 years, from Chicago, Ill., was seen in Nov. 1952. She stated that four years previously an asymptomatic, bluish, mottled discoloration of the legs had developed, which quickly spread to involve the entire lower extremities and arms. The mottling was worse with cold weather but warmth caused no particular change. In the past three years edema and painful "blood blisters" had developed, which progressed to ulcerations involving the feet, ankles and legs. The initial episode of ulceration occurred during the winter and the ulcers recurred most frequently and severely during the cold months, so that she was advised to move to a warmer climate. The edema of the legs and feet would subside on elevation but a variety of prior treatments for the ulcerations, including oral and local antibiotics, roentgen treatment, cortisone, elastic bandages, elastic-paste boots and several weeks of rest in bed had resulted in little benefit.

She had had the best relief from pain and ulceration while lying a great deal in the sun for six months in 1952, but then a severe exacerbation of ulceration and edema developed and subsequently five lumbar sympathetic ganglion blocks with procaine hydrochloride had been of decreasing benefit.

Approximately one year previously, paresthesias had developed in the lower extremities and for three days she had had temporary "paralysis" of the right leg. Since then she had had some intermittent subjective numbness in both lower extremities. With exposure to cold she had noted numbness and

TABLE 1.—*Livedo Reticularis with Winter Ulcerations*

Patient	Age, years, sex	Duration of livedo	Duration of ulceration	Location and description of ulcerations	Microscopic examination	Bilateral lumbar sympathectomy	Miscellaneous
1	24 F	4 years	3½ years	Small, superficial, irregular ulcers of ankles. Scars at sites of former ulcers over feet and legs (fig. 1*a*)	L. foot: Arterioles in dermis had thickened walls and thrombi occluding lumen. Vein at dermal-subcutaneous junction showed thickened wall, perivascular infiltrate and occlusion of lumen by thrombus (fig. 1*b*, *c*, *d* and *e*)		Hexamethonium (bistrium bromide) treatment during and after hospitalization seemed to be of benefit in more rapid healing of ulcerations
2	42 F	4 years	2½ years	Ischemic ulcer of left fourth toe		Two right lumbar ganglia and three left lumbar ganglia and respective intervening chains	B.P. 200/116. Hexamethonium (bistrium bromide) trial resulted in less livedo and in warming of toes
3	45 F	5 years	2 years	Toes cyanotic and cold with crusted ulcers on tips of toes (fig. 2*a*)	R. leg: Arteriole in subcutaneous tissue revealed hyalinization of wall and thrombosis with obliteration of lumen		Raynaud's. B.P. 158/108
4	30 F	7 years	Same	15–20 scars of prior ulcerations on ankles			
5	22 F	All life	6 years	Scars of prior ulcerations on legs			Acrocyanosis. Cold feet and hands
6	35 M	8 years	2 years	Cyanosis of several right and left toes. Superficial ulceration of right leg		Right: Greater and lesser splanchnic-nerve resection with removal of portion of celiac ganglia and L2-L3 ganglia and intervening chain. Left: Similar splanchnic and celiac-ganglia resection and L1-L2 ganglia and intervening chain	B.P. 165/105
7	37 F	11 years	Several yr.	Scars of prior ulcers on both feet			Raynaud's
8	36 F	All life	8 years	Ulcer 4 x 2 cm. on left leg (fig. 2*b*)	L. thigh normal. L. leg: Many small arterioles with completely or partially obliterated lumina	Right: Two ganglia and intervening chain in region L1. Left: Three ganglia and intervening chain in region L1	

				tially obliterated lumina		ganglia and intervening chain in region L1	
9	45 F	Since childhood	20 years	Atrophic scars on anterior aspects of both legs			Raynaud's
10	48 F	1 week	2 years	Scars on tips of toes			Raynaud's
11	50 M	3 months	Same	Cyanosis of several right and left toes. Ulceration of tip of left third toe		L1-L2 ganglia and intervening chain	
12	26 F	8 years	1 year	Small punched-out ulcers on both legs	L. calf: Small arterioles revealed proliferation of intima and occlusion		
13	25 F	10 years	3½ months	2/51: Cyanosis of several right and left toes. Ulcer of plantar surface of left first toe		Bilateral lumbar sympathectomy elsewhere in 8/50, but ulcers of toes recurred	Raynaud's; hyperhidrosis. Typhoid vaccine of benefit
			4 days	5/51: Cyanosis of left first toe. Ulcer of right fifth toe			Typhoid vaccine of benefit
			6 months	11/51: Ulcer of tip of right fifth toe			Typhoid vaccine of benefit
	29		1 month	1/55: Superficial ulcer of right fifth toe			Local treatment to ulcer including red-cell paste. B.P. 158/98
14	25 M	4 years	3 years	1936: Scars of prior ulcerations of feet and ankles. One ulcer on dorsum of right foot. 1951: Atrophy of skin of lower legs with prominent veins. No ulceration			Cold feet
15	54 M	2½ months	Same	1954: Ischemic ulcer of right anterior leg and medial ankle	L. leg: Nonspecific dermatitis		1946: Traumatic occupational occlusive arterial disease with secondary Raynaud's phenomena right hand. Treatment: Right second thoracic sympathectomy. Improvement of symptoms afterward
16	54 M	4 years	Same	Ulcerations on several toes			Acrocyanosis. Arteriosclerosis. B.P. 150/110
17	55 M	1½ years	6 months	Ulcer on right third toe			Cold feet and legs. B.P. 180/105
18	18 F	Many yr.	2 years	Scars and crusted ulcers on lower legs and feet			B.P. 140/92

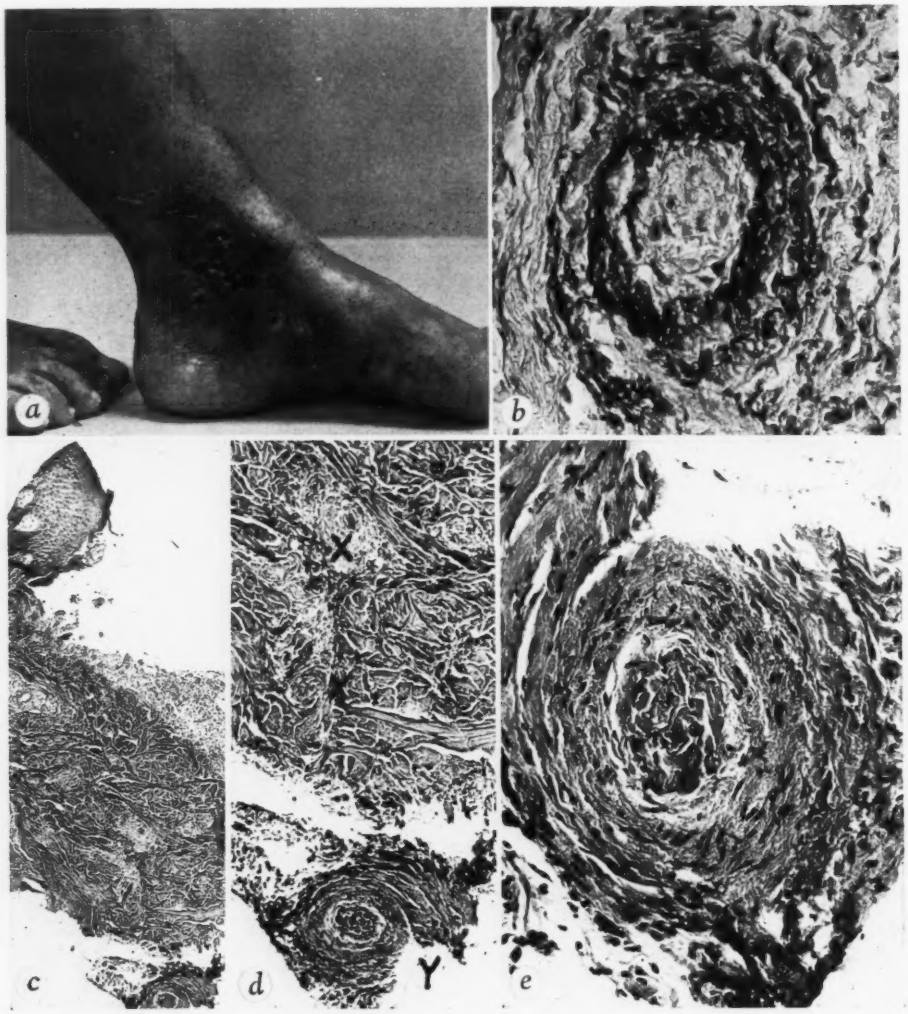

FIG. 1 (case 1, table 1). Case of livedo reticularis with winter ulcerations (figures have been reduced from stated magnification).

a. Note livedo reticularis, ischemic infarctive ulcerations and depigmented and pigmented scars.

b. Left ankle, lower dermis. Small arteriole shows some thickening of the wall and occlusion of the lumen by a thrombus (elastin H; ×625).

c. Left ankle, edge of ulcer. Dilatation of capillaries and lymphatics under the base of the ulceration. Occlusion of several vessels in the mid and lower dermis and occlusion of a large vein at the dermal-subcutaneous junction (hematoxylin and eosin; ×35).

d and *e*. Higher magnifications of dermal subcutaneous vessels shown in *c*. *d*. Note arterioles at X which reveal occlusion of the lumina by thrombi and similar occlusion of vein at Y (hematoxylin and eosin; ×100). *e*. Thickening of venous wall, thrombosis of the lumen and moderate nonspecific perivascular infiltrate (hematoxylin and eosin; ×300).

ome color changes of her hands and feet but no efinite Raynaud's phenomena.

The past history and family history were not ignificant. She smoked one-half package of cigarets aily.

Examination revealed a blood pressure of 130 mm. f mercury systolic and 80 diastolic. Livedo reticuaris involved the entire lower extremities, buttocks nd forearms. The feet were warm and there were umerous ulcerations and slight edema of both nkles. Pigmented scars of the feet and legs remained t sites of prior ulceration (fig. 1*a*). There were no aricose veins or evidence of venous insufficiency, nd the arterial pulsations in the lower extremities were normal. The results of the remainder of the examination, including the neurologic examination were not unusual.

Laboratory examination revealed a normal or negative urinalysis, erythrocyte, leukocyte and leukocyte differential blood counts, hemoglobin, sedimentation rate (Westergren), serologic test for syphilis and chest roentgenogram. A basal metabolic rate was −5 per cent. Skin temperature studies revealed very little or no change in a cold room, but normal increase of skin temperature in a hot room. Two trials of 25 mg. of hexamethonium (bistrium bromide) by subcutaneous injection on two occasions revealed little or no rise in the skin temperature. Microscopic examination of a specimen for biopsy at the edge of an ulcer of the left lateral ankle revealed a large vein at the dermal-subcutaneous junction which had thickened walls, slight perivascular infiltrate and thrombosis of the lumen. In the dermis were several vessels, especially some arterioles, which revealed thrombosis (fig. 1*b*, *c*, *d* and *e*).

The patient entered a hospital on Dec. 2, 1952, and was treated with elevation of the lower extremities, local antiseptic wet dressings and rest in bed. From December 8 until December 13 she received 25 mg. of bistrium bromide subcutaneously every eight hours. When she was dismissed on Dec. 13, 1952, the ulcerations were 90 per cent healed. She was advised to use elastic supportive bandages for the lower extremities and continue with bistrium injections at home.

In January, 1953 (one month later), the patient wrote that the previous ulcers had healed, no new ulcers had developed and there was no edema or pain. She continued to use the elastic bandages and bistrium injections. In February, 1953, she discontinued the bistrium and, although there was an increase in perspiration, no ulcerations occurred. During the summer and fall of 1953, several ulcers developed on the feet and legs, but the addition of bistrium bromide injections, 25 mg. every eight hours for one week, seemed to result in rapid healing of the ulcers. Her last letter in October, 1953, stated that she had no ulceration, edema or pain and she continued to use elastic supportive bandages

Case 2. A white, married housewife, aged 42 years, from Kentucky was seen in June, 1954. She stated that during February and March, 1950, she had had one episode of pain and discoloration of the right third toe which subsided spontaneously in a few days. During May, 1950, she had the sudden onset of pain and purple discoloration in the same toe which became progressively worse and in June, 1950, she underwent right lumbar sympathetic ganglion block with procaine hydrochloride continuously for 36 hours. The pain was relieved and the normal color of the toe was restored. She was advised to use Priscoline orally and had no recurrence until February, 1951, when a progressive discoloration was noted to involve all the toes, both feet and the right ankle. The discoloration was worse during the winter and on exposure to cold weather. During the past two winters ulcers had developed on the right great and left fourth toes. The ulcers would start during the winter and had persisted into the summer, but never had started in the summer months. During the prior winter she had noted occasional burning and redness of the tips of the fingers with exposure to cold but no definite Raynaud's phenomena.

There was no history of claudication in the lower extremities on walking, edema of the legs or thrombophlebitis.

The past history and family history were not significant except that five years previously she had been told that she had hypertension and for eight years she had had irritable colon which responded well to treatment. Roentgenographic examinations of the intestinal tract and proctoscopic examination had been normal. She had smoked one-half package of cigarets daily until stopping four years previously.

Examination revealed a blood pressure of 170 mm. of mercury systolic and 100 diastolic. Funduscopic examination revealed narrowing and sclerosis, grade 1, of the retinal arterioles. A faint precordial systolic murmur, grade 1, was audible. There was a mottled, bluish discoloration of both feet, intense over the toes and less marked over the right ankle. The toes of both feet felt cold to touch. The left fourth toe was entirely blue and had an ischemic ulcer. All arterial pulsations in the lower extremities were good. There were no signs of varicose veins or venous insufficiency.

Laboratory examination revealed negative or normal erythrocyte, leukocyte and leukocyte differential counts, roentgenograms of the chest and colon (barium enema), sedimentation rate (Westergren), fasting blood sugar, blood urea and cholesterol determinations. A roentgenogram of the thighs and a simple roentgenogram of the abdomen revealed no vascular calcification in the thighs or abdominal aorta. The basal metabolic rate was −5 per cent. The patient entered a hospital on July 4, 1954. A trial of 25 mg. of hexamethonium (bistrium bromide) seemed clinically to result in less marked livedo and

in warming of the toes, but skin-temperature studies did not show a significant rise in temperature. The ingestion of an alcohol test dose and hot-room testing revealed a normal rise of skin temperature. The patient did not wish to continue with a therapeutic trial of hexamethonium injections but preferred sympathectomy. She did not desire to have the more extensive subdiaphragmatic sympathectomy used in the treatment of hypertension as well.

On July 10, 1954, bilateral lumbar sympathetic ganglionectomy and trunk resection was performed with removal of three left lumbar ganglia and intervening chain and two right lumbar ganglia and intervening chain. Postoperative examination revealed the feet to be warmer and the livedo much improved. However, cyanosis of the left third and fourth toes still remained. No information about this patient has been received since her dismissal after the operation.

Livedo reticularis and winter ulcerations associated with it are illustrated in figures 1 and 2.

Analysis of Clinical and Laboratory Data

There were 18 patients with livedo reticularis and primarily winter ulcerations, of whom 12 were women and six were men. All were of the white race. Of the seven married women all had one or more children. Thirteen (72 per cent) of the 18 patients were between the ages of 20 and 49 years, inclusive. The youngest patient was 18 years old and the oldest was 55 years old.

When first seen at the clinic because of ulceration, three patients were living in Canada, three in Minnesota, two in Michigan, two each

FIG. 2. Cases of livedo reticularis with winter ulcerations (figures have been reduced from stated magnification).

a (case 3, table 1). Note prominent livedo reticularis, especially of the lower extremities, and ulceration of the distal portions of the toes.

b (case 8, table 1). Left calf: Irregular, indolent, "punched-out" ulceration which clinically appears not unlike ulcers suspected to be of factitial origin or erythema induratum.

also in Iowa and Illinois and the others were one each from Arizona, Kentucky, South Dakota, Texas, Wisconsin and Wyoming.

Seven of the women were full-time housewives; the other women had occupations in which they were not exposed to unusual degrees of heat or cold. The six male patients had a variety of occupations, none of which seemed related to excessive exposure to heat or cold. Approximately two-thirds of the patients smoked an average of one package of cigarets daily; the remainder were nonsmokers. The past history in this group of patients was relatively noncontributory. No pertinent history of illnesses such as tuberculosis, syphilis and so forth was elicited concerning the patient or the patient's family. Raynaud's phenomena had been noted in 6 of the 18 patients (one third) and in another third there was a history of sensitivity to cold such as "cold feet" during the winter or paresthesias of the extremities with cold weather. In the remaining third of the patients, symptoms or signs of intolerance to cold were not recorded. Several patients had noted prominent hyperhidrosis, especially of the palms and soles. There was no history of lead or arsenic intoxication.

The present history of these patients was similar to the history from patients with livedo reticularis and summer ulcerations except for the seasonal difference, and a typical sequence of events comprising the present history is included in the part of the report dealing with summer ulcerations. The results of physical examination in this group of patients were similar to those in the summer group of ulcerations except for four findings. Several patients with winter ulcerations had acrocyanosis in addition to the livedo reticularis, and digital arterial occlusion with associated ulcerations of the toes was noted in seven patients, of whom three had Raynaud's phenomena. Hypertension was noted in several patients with winter ulcerations, as recorded in table 1. In several of these patients hypertension would not be unusual considering the age of the patient, but several relatively young patients had severe hypertension (for example, patients 2 and 6). Several patients in this group had unilateral or bilateral absence or marked diminution of pulsation of the dorsalis pedis or posterior tibial arteries. This usually occurred in patients with arterial occlusion of the toes.

Laboratory examinations, as in the summer group of ulcerated livedo reticularis subsequently described, revealed essentially negative or normal results of urinalysis, erythrocyte and leukocyte counts and hemoglobin. The sedimentation rate (Westergren) was usually normal. A basal metabolic rate was within normal limits in three patients. Chest roentgenograms were essentially normal in all of the patients. Cryoglobulin and lupus erythematosus blood test in one instance were negative. Cultures for bacteria and fungi from the chronic ulcerations in one patient revealed normal bacterial flora and no fungi. Histopathologic examinations of cutaneous specimens for biopsy, usually from ulcer sites, are recorded in table 1 and a comparison of the histopathologic features of winter and summer ulcers is presented in part 3. The findings were essentially similar to those recorded for summer ulcerations. No fungous elements were noted.

Cutaneous-temperature studies in several patients revealed findings similar to those in the summer group of ulcerations, in that there was generally a normal initial cutaneous temperature of the fingers and toes with a normal rise of cutaneous temperature after ingestion of alcohol, hot-room exposure and lumbar sympathectomy. Hexamethonium (bistrium bromide) treatment of several patients did not seem to result in a rise of cutaneous temperature by measurable means, but clinically the livedo seemed less marked afterward, the feet seemed warmer and the ulcers seemed to heal more rapidly.

Treatment

Of the 18 patients with winter ulcerations associated with livedo, five patients underwent bilateral lumbar sympathectomy (the sympathectomy in case 13 was not done at the clinic), 11 patients were treated with or advised to have rest in bed, elastic supportive bandages for the lower extremities, local antiseptic and

TABLE 2.—*Summary of Some Findings in Twelve Patients with Summer Ulcerations**

Patient	Age, years	Duration of Livedo	Duration of Ulceration	Location and Description of Ulcers	Microscopic Examination	Bilateral Lumbar Sympathectomy
1†	31	7 years	Same	1946: Scars on anterior legs, ankles and plantar surface foot. 1948: About 1 year after sympathectomy; ulcer 2 x 2 cm. on medial malleolus. Ischemic and infected	1946: Thigh: Arteriole at dermal - subcutaneous junction thickened and lumen thrombosed. Calf: Similar findings	L2-L3. Recurrence of ulcers 4–5 months after operation and in late summer for 6 years. Ulcers fewer, more superficial and less persistent after operation
2†	40	Not stated	15 years	Scars and hemorrhagic spots on both legs. Ulcers on dorsa of both feet and ankles	Leg: Arterioles in dermis revealed thickening of wall with narrowed or obliterated lumina. Subcutaneous vein had thickened wall, intimal proliferation and obliteration of lumen	
3	47	7–8 years	Same	Crusted infected ulcers on ankles	None	
4	23	1½ years	About 16 months	1942: Small focal hemorrhagic ulcers about ankles. 1951: Pigmentation and scars on feet, ankles and lower legs	None	
5	31	Not stated	13 years	Thickening, scaling, crusting and hemorrhagic spots over dorsa of feet and anterior aspect of legs	Leg: Arterioles in dermis and subcutaneous tissue showed slight thickening of walls. Large vein in subcutaneous tissue had thickening of wall and obliteration of lumen	
6	54	7 years	4 years	Tiny ulcer on lateral aspect of lower leg	None	
7	27	4½ years	4 years	Scars on dorsa of feet and ankles; atrophy of skin about ankles; 1–2 cm. punched-out ulcers with necrotic bases on plantar surfaces of feet	None	L2-L4. Recurrence of ulcers after 1 month and for subsequent 2 years. Patient believed operation was not beneficial
8	34	7 years	Same	Scars on feet and ankles. Irregular ulcers with necrotic bases on dorsum of foot and sole	Ankle: Several arterioles in dermis had thickening of walls, intimal proliferation and occlusion of lumen	
9‡	36	23 years	Same	Scars, purpuric spots and crusted ulcers about ankles	None	L1-L5. Ulcers recurred after 7 months during subsequent spring and summer months

TABLE 2.—*Continued*

Patient	Age, years	Duration of Livedo	Duration of Ulceration	Location and Description of Ulcers	Microscopic Examination	Bilateral Lumbar Sympathectomy
10	17	2 years	1 month	1942: Faint livedo, petechiae and pigmentation over toes, dorsa and soles of feet and legs. No ulceration. 1947: 0.5 cm. infected ulcers on both ankles	1942: Leg: Slight thickening of walls of larger arterioles but no occlusion. 1947: None	L3. Recurrence of ulceration after 2 months. Patient stated operation had been of no value
11	35	Many years	12 years	Crusted infected ulcers and scars about ankles and dorsa of feet (fig. 3*a*)	Ankle: Intimal proliferation and occlusion of lumen of arterioles in dermis by thrombi. Thickening and hyalinization of some walls of arterioles. Fibrosis and thickening of vein at dermal-subcutaneous junction and obliteration of lumen (fig. 3*b*)	
12§	47	1 year	5 years	Several discrete and confluent irregular ulcers of ankles. Pigmentation and scars	Ankle: An arteriole in the subcutaneous tissue showed thickened wall, intimal proliferation and narrowed lumen	

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† Complete case histories, including pictures showing the appearance of the ulcerations and histopathologic examinations, of patients 1 and 2 are reported.[1]

‡ Patient presented at meeting of Minnesota Dermatological Society, Sept. 26, 1943.[38]

§ Patient presented at meeting of Minnesota Dermatological Society, Sept. 12, 1954.[39]

red-blood-cell paste to the ulcers and occasionally typhoid vaccine, and in addition, two patients received hexamethonium injections.

We have been unable to learn the results of the patients treated medically without hexamethonium. Little is known of the eventual results of the patients treated with sympathectomy. One patient (number 13) with digital artery thrombosis and ulceration of the toes, seemed to have no permanent benefit, since ulcers continued to recur after the operation. Both patients treated with hexamethonium seemed to have some benefit and it has been our impression that the use of this drug in other patients with livedo reticularis and ulcerations, not included in this report, was worth while.

B. Livedo Reticularis with Summer Ulcerations

Several patients have been at the clinic who had ulcerations similar to those seen in livedo reticularis and chronic pernio but beginning only or primarily during the warm months of the year. From the approximately 400 records of patients with livedo reticularis and pernio which were reviewed, 12 patients with this entity were found.

A report of the findings in one patient is presented, and table 2 summarizes some of the findings in all 12 patients. An initial report of this new syndrome was published previously by us.[1]

Report of Case (Patient 11, Table 2)

A white housewife and bookkeeper, aged 35 years, from Detroit, Mich., was seen in July, 1952. For

FIG. 3 (case 11, table 2). Case of livedo reticularis with summer ulcerations. *a*. Note irregularly shaped ulcerations, pigmentation and scars confined primarily to the ankle regions and dorsa of the feet. Distinct border between involved and uninvolved portion of foot is not uncommon.

b. Right ankle. Increased number and dilatation of capillaries and vessels in upper corium. Thickening of arteriolar and venous walls and narrowed or obliterated lumina especially noted at X (hematoxylin and eosin; ×30).

many years she had noted an asymptomatic, bluish red discoloration of the arms and legs when exposed to cold weather, but in the summer of 1940 a similar confluent eruption developed, which was confined to the lower extremities from knees to ankles followed by residual brownish hyperpigmentation. Two weeks afterward, there developed a burning sensation of the ankles, swelling of both feet and small red spots over the lateral malleoli of the ankles which subsequently became "blisters" and ulcers with drainage of serosanguineous fluid, crusting and finally healing. The entire episode from appearance of hemorrhagic spots to healing covered four to six weeks.

From 1940 to 1944 the patient was never free of ulcerations for more than four weeks and the painful ulcerations started predominantly during the summer months. After 1944 further ulcers did not develop until September, 1950, when necrotic ulcers of the ankles again developed, which only cleared temporarily with elevation and local treatment.

In 1951 and 1952 paresthesias developed with pain and burning in the left foot and several toes, and afterward the patient had a permanent subjective hypalgesia in these areas. About six times in the prior two years she had noted cramps in the right calf on first waking in the morning but these disappeared on further exercise.

The family history revealed that two siblings and a distant nephew had tuberculosis, another sibling had rheumatic heart disease, the patient's mother had gallbladder and heart disease while her father had hypertension. She smoked one package of cigarets daily.

Examination revealed a blood pressure of 104 mm. of mercury systolic and 60 diastolic. There was a faint livedo reticularis of the arms which was of variable intensity. From knees to ankles there were hyperpigmented areas, and on the sides of the ankles and dorsa of the feet were several ulcers, in areas of livedo reticularis, some crusted, with surrounding inflammation and edema (fig. 3*a*). There were scarring and pigmentation at sites of former ulcers and a few dilated superficial venules were evident over the legs but no large varicose veins. Arterial pulsations were all good.

Complete neurologic examination revealed only a subjective decrease of pain, touch and temperature in several left toes and medial aspect of the left foot which was thought to be a mononeuritic multiplex type involvement seen in occlusive arterial disease affecting the vasa vasorum.

Laboratory examination revealed flocculation re-

action for syphilis, chest roentgenogram, platelet count, bleeding and clotting time to be negative or normal. Cultures of the ulcers revealed pseudomonas organisms. Microscopic examination of a cutaneous specimen for biopsy from the right ankle revealed increased number, dilatation and tortuosity of subepidermal capillaries and intimal proliferation and occlusion of the lumina of dermal arterioles by bland amorphous thrombi. There were thickening, hyalinization and nonspecific cellular infiltration of some arteriolar walls. A large vein at the dermal-subcutaneous junction had fibrosis and thickening of the walls with obliteration of the lumen (fig. 3*b*). The results of other pertinent laboratory examinations were not remarkable.

On Aug. 1, 1952, the patient underwent left lumbar block with absolute alcohol performed at L-2. The pain of the ulcers of the left lower extremity was relieved and the extremity became warm and comfortable. Elevation of the legs and mild local treatment were advised.

A right lumbar block was not performed, and on Aug. 18, 1952, the ulcers were healed. The patient was dismissed and 1 month later, although pain in the left foot had recurred, no ulcers were present.

A letter in May, 1953, from a dermatologist reported that he had seen the patient and that she had no active ulcers, only residual pigmentation and scars.

Analysis of Clinical and Laboratory Data

All patients who had summer ulcerations were white women. Four were single and eight were married. All the patients but three were in the age group of 21 through 40 years. The oldest patient was aged 54 years, and the youngest was aged 17 years.

All the patients lived within 500 miles of the clinic; four patients were living in Illinois, two resided in Michigan, and the others were one each from Kentucky, Iowa, Wyoming, Kansas, Minnesota and Ontario, Canada.

None of the patients were employed in an occupation which exposed her to excessive heat or cold; eight were housewives, two were employed in clerical office work, one was employed as an assembly worker and one patient was a student.

Four patients were nonsmokers, while seven patients were mild to moderate smokers of about one package of cigarets or less daily. A history of smoking was not recorded in one case.

The past history in the patients as a whole was noncontributory. A history of a relative or relatives having had tuberculosis was present in three cases but none of the patients had had tuberculosis. A vague history of frostbite as a child was reported by one patient.

Several patients believed that they were "nervous," and hyperhidrosis of the palms or soles was noted by a few patients. In no case was a history of syphilis or Raynaud's phenomena reported. There was no history of intoxication by lead or arsenic.

The present history of each patient was remarkably similar. Other than the seasonal occurrence, the history in patients with summer and winter ulcerations is essentially similar. A typical sequence of events was, in a patient with summer ulcerations, as follows: A variable amount of livedo reticularis over the body, especially of the lower extremities was noted for several weeks, months or years before onset of the ulcerations. The livedo was usually more prominent in the winter than in the summer. During the spring, or summer, edema of the feet and ankles developed which was most severe at the end of the day and less in the morning after rest. Shortly after the development of edema there occurred red to bluish infarctive areas over the legs, ankles, dorsa of the feet and soles which would either disappear spontaneously, or ulcerations would occur at these sites after several weeks. The infarctive lesions and ulcerations would appear spontaneously and no prior insect bite or trauma could be definitely incriminated. Healing would result in an atrophic, pigmented or depigmented scar. These ulcers would be very painful and resistant to most medical forms of treatment, both local and systemic. The entire course from onset of infarcts to ulceration and healing would be usually one and one half to three months. New ulcerations would continually develop during the summer, but with cold weather the ulcers would tend to heal and not recur, so that during the winter the patient would be free of ulcerations or markedly better. In the patients with winter ulcerations, of course, the reverse was true, in that the ulcerations would primarily occur during the winter and tend to heal in the

summer months. Occasionally a summer ulceration would persist throughout the winter and occasionally an ulcer would start during the winter months, but this was the exception in the patients with primarily summer ulcerations.

The results of examination of the patients, other than the ulcerations and presence of livedo reticularis, were essentially normal in every instance of summer ulcerations. No unusual body habitus or undue obesity was noted. The blood pressure was essentially normotensive in all of the patients. Active ulcerations or scars of previous ulcerations were present mostly about the ankles, dorsa and soles of the feet and on the lower part of the legs. No ulcers were present above the knees, on the upper extremities, or any other part of the body, regardless of the distribution of the livedo. The initial lesion would appear as a painful, red to bluish infarctive or hemorrhagic area. The ulcers were generally irregular in shape and of various sizes from 0.5 cm. to 1 or 2 cm. in diameter and were deep or superficial, discrete or confluent. Many were infected and had purulent drainage. The ulcerations clinically at times suggested ulcers of factitial origin or erythema induratum. Edema of the feet and ankles was usually present to some degree. In no patient were there noted significant varicose veins or evidence of chronic venous insufficiency. Arterial pulsations were normal in the lower extremities in all patients except one (patient 7) who had a diminished right dorsalis pedis pulsation. Occlusive arterial disease was not suspected or demonstrated in any patient. There was no history or evidence of digital arterial thrombosis or superficial phlebitis in any patient.

Laboratory examinations revealed an essentially normal urinalysis, erythrocyte and leukocyte counts and hemoglobin. Sedimentation rate by the Westergren method usually revealed normal results. The serologic reaction for syphilis was negative in every case. The chest roentgenogram was essentially normal in all of the patients.

Although none of these patients was suspected of having hyperthyroidism, hypothyroidism or myxedema, basal metabolic rate determination in two patients revealed results of +12 and −14 per cent. Bacteriologic culture from an ulcer in one patient revealed pseudomonas organisms.

Treatment

Of the 12 patients in the summer group of ulcerations with livedo reticularis, six were advised to have rest in bed, elastic supportive bandages for the lower extremities and mild local therapy to the ulcerations, and one patient, in addition, used hexamethonium therapy; four patients underwent bilateral lumbar sympathectomy and one patient underwent unilateral lumbar alcohol block. No information has been received as to the results in the patients treated medically without hexamethonium. The patient with the unilateral lumbar alcohol block seemed to have more rapid healing of the ulcerations, and she had only healed scars 10 months afterward when she was seen by a dermatologist elsewhere. The results of lumbar sympathectomy are noted in table 2. Usually little permanent benefit was gained from sympathectomy.

Patient 2, table 2, seemed to gain considerable benefit from hexamethonium treatment and it has been our impression that other patients with livedo reticularis and primarily winter ulcerations (table 1) seemed to benefit from hexamethonium.

3. Comparison of Histopathologic Features of Winter and Summer Ulcers

Histopathologic Examination

Histopathologic examination was done usually from biopsies at the sites of ulcers in five patients with winter ulcerations and seven patients with summer ulcerations.

Of these patients with ulcerations the following was noted: The epidermis usually revealed acanthosis and proliferation of the rete pegs about the site of the ulcer. In several cases histopathologic examination revealed granulation tissue, edema and nonspecific cellular infiltrate with little or very slight intimal proliferation and thickening of small arterioles. Dilated subepidermal capillaries, lymphatics and venules were noted in the majority of the

cases. In four of the five patients with winter ulcers and four of the seven patients with summer ulcers on whom microscopic examination was performed, there were thickening of the wall of the arterioles of the cutis and subcutaneous tissue and occlusion of these vessels, and of these, in two cases each, of both the summer and the winter group, the arterioles revealed occlusion by a thrombus. In the biopsies of one patient with winter ulcers and three patients with summer ulcers, there were veins evident in the subcutis which showed thickening of the walls and obliteration of the lumen of the vein. There was usually a mild to moderate nonspecific infiltrate in the cutis which was usually perivascular, with some infiltration of the occluded arterioles and veins. There was relatively little panniculitis or fibrosis of the subcutaneous fat and no giant cells were evident in any section. Elastic-tissue stains generally revealed that the internal elastic limiting membrane of the intima of the arterioles was undamaged. Fragmentation of the elastic fibers in the corium was noted in several specimens. Iron stains for hemosiderin were positive in more than 50 per cent of the cases. However, in all these cases the specimen for biopsy was removed from the lower extremities, where some hemosiderin can be demonstrated in persons without peripheral vascular disease or clinical evidence of venous insufficiency.

Hotchkiss-McManus or periodic acid-Schiff stain revealed that several of the thickened arteriolar walls in various sections were stained intensely with this stain. No fungous elements were noted. Maresch modification of the Bielschowsky stain for reticulum fibers and Bodian silver stain for nerve fibers revealed no increase in any case. Stains for amyloid did not reveal presence of amyloid in any case and the Giemsa stain did not reveal an abnormal number of mast cells. There was no histopathologic evidence for periarteritis nodosa or syphilis in any section.

Histopathologic Differential Diagnosis

There are several diseases which resemble to a varying degree the histologic picture in livedo reticularis. Pernio, nodular vasculitis, venous insufficiency and sometimes erythema induratum may be especially difficult or impossible to differentiate by histopathologic examination. Pernio[27] can have a similar angiitis, but may have a good degree of panniculitis and giant cells. Nodular vasculitis[30-34] may show a vasculitis of both arteries and veins with varying degrees of thickening and obliterative change; however, fibrosis and atrophy of the subcutaneous tissue and foreign-body giant cells may be more prominent. In chronic venous insufficiency of the lower extremities, both arterioles and veins may reveal intimal proliferation and thickening of the walls as in cases of livedo reticularis. Erythema induratum classically shows typical tubercles but in about 30 per cent of cutaneous biopsies, examination shows a nonspecific granuloma and vasculitis which is not diagnostic.[30] Hypertensive ischemic ulcers reveal only involvement of the arterioles with such changes as thickening of the walls, decrease of the size of the lumen and some periarteritis.[29]

Superficial thrombophlebitis, erythema nodosum and panniculitis of Weber-Christian do not usually cause ulceration, but might be considered in the biopsy of a nonulcerated lesion. Thrombophlebitis involves only the veins with occlusion of the lumen, inflammatory infiltrate of the wall of the vein and varying amounts of periphlebitis. Erythema nodosum may show an acute inflammatory reaction in the corium and subcutaneous tissue with polymorphonuclear leukocytes, fat-replacement atrophy and Miescher granuloma formation, but thrombosis of the vessels and proliferative changes of the walls are not unusual. Secondary thrombophlebitis and a tuberculoid reaction may be found in erythema nodosum. Panniculitis of Weber-Christian generally reveals an inflammation primarily of the fat, and minimal changes, usually in the vessels.

In summary, the histopathologic picture of summer ulcerations or winter ulcerations with livedo reticularis reveals no essential difference in the type or degree of vessel involvement. Arterioles generally showed thickened walls, intimal proliferation and occlusion of the lumen, sometimes by a thrombus. Several

veins in the summer group and one in the winter group showed thickening and infiltration of the wall with obliteration of the lumen.

Comment

We have studied a group of patients who have idiopathic livedo reticularis and ulcerations of the legs or feet beginning both during the winter and summer months of the year. The patients had noted the livedo reticularis for several weeks or years before the onset of the ulcerations. Although the livedo was usually worse during the winter, in one group the ulcerations were primarily during the warm months and healed after the onset of cool weather. Edema of the feet or ankles was associated with and usually preceded the hemorrhagic, infarctive lesions in both winter and summer ulcerations. However, it was our impression that the edema was a more prominent feature in those patients with summer ulcerations than in those with winter ulcerations. Painful ulcers subsequently developed at these sites, which might heal after several months, but new ulcers recurred during the summer or warmer months of the year in the summer group of ulcerations in contrast to the healing of the ulcers during the summer in the usual instance of winter ulcerations. Occasionally a patient with primarily winter ulcerations would develop ulcerations during the summer months, such as was reported by patient 1 in the winter group. The summer ulcerations generally seemed to be more resistant to treatment than the winter ulcerations. The associated edema and increased vasodilatation during the summer may be a factor in the increased frequency of ulcerations during the summer months in certain individuals. However, the ulcers did not have the features of typical stasis ulcers. It is possible that pressure from edema of the skin might increase the localized ischemia of the skin and further the development of ulceration.

A review of the literature concerning livedo has revealed that the occurrence of livedo reticularis and ulcerations during the warm months of the year has not been a recognized syndrome. Ebert[5] described the findings in a woman, aged 33 years, which seems to be the only similar recorded case. Some of the pertinent features in this patient are noted in the histopathologic portion of part 1 in this report. Ebert expressed the belief that the ulcerations were most probably tuberculoid, although there was no clinical or laboratory evidence of tuberculosis. Ebert's patient could represent a case of livedo reticularis with summer ulcerations similar to the cases in the group that we are reporting.

Histopathologic studies from biopsies at ulcer sites in the patients with summer ulcerations often revealed occlusion of the arterioles and veins, but these findings were not unique for the cases with summer ulcerations, since similar histopathologic findings were seen from biopsies of winter ulcerations with livedo.

The edema preceding the onset of the ulcers would seem to indicate a stasis factor and the biopsies revealed involvement of veins as well as arterioles. Kulwin and Hines[40, 41] reported pathologic changes in the cutaneous arterioles and veins not too dissimilar from our findings in patients with chronic venous insufficiency with edema even in areas of normal-appearing skin of the lower extremities.

Treatment of these patients with winter and summer ulcerations by sympathectomy did not seem of permanent value according to the follow-up information which we possess. Medical treatment employing local antiseptic dressings, powdered red blood cells, rest in bed with elevation of the extremities, elastic supportive bandages, and a trial of the hexamethonium drugs seems to be the best therapy. Typhoid vaccine treatment seemed to be beneficial in several of these patients with livedo reticularis and ulceration, especially in patient 13, table 1.

Summary and Conclusions

A brief summary of the medical literature concerning livedo reticularis is presented, especially in reference to the occurrence of ulcerations. In reviewing the records of approximately 400 patients with livedo reticularis and pernio seen at the Mayo Clinic in the past 10 years, 18 patients with winter ulcerations and 12 patients with primarily summer ulcerations and livedo reticularis were found. The

clinical and histopathologic data in these patients form the basis of this report.

The clinical and histopathologic findings in these two groups of patients are very similar. All of the patients in the summer group and two thirds of the winter group were women. Hypertension, Raynaud's phenomena, acrocyanosis, digital artery thrombosis and occasional absence of dorsalis pedis and posterior tibial arterial pulsations were noted only in the patients with winter ulcerations. There was no difference in the appearance or location of the ulcerations occurring on the legs, ankles or feet other than the ulcerations secondary to occlusion of digital arteries in the winter group. Edema of the legs and feet was often an associated feature in this group with livedo and ulcerations. The edema was a more prominent feature in the patients with summer ulcerations than in those with winter ulcerations.

Histopathologic studies revealed similar changes of occlusion in the arterioles and veins which were not diagnostic. No evidence of tuberculosis, syphilis or periarteritis nodosa was discovered as a causal feature in any case.

Therapy stressing rest in bed, elastic supportive bandages to prevent edema, and hexamethonium was the treatment of choice. Sympathectomy seemed of little permanent value in the majority of patients.

Addendum

Since this paper was written it has been brought to our attention that Yorke and Klaber have reported a case not unlike those with summer ulcerations discussed here (Yorke, G. A. [for Dr. Robert Klaber]: Asphyxia reticularis multiplex [Unna]. Proc. Roy. Soc. Med. **37:** 640, 1944).

Summario in Interlingua

Idiopathic livor reticular pote esser associate con ulcerationes del extremitates inferior comenciante primarimente durante le plus calide menses del estate, a parte le plus usual occurrentia de ulcerationes durante le menses del hiberno. Ulcerationes de estate es apparentemente un nove e rar entitate. Illo ha multe characteristicas histopathologic e clinic que es simile a illos del ulcerationes de hiberno. Hypertension, phenomenos de Raynaud, acrocyanosis, e thrombosis de arterias digital esseva notate solmente in patientes con ulcerationes hibernal, durante que edema del gambas e pedes esseva un characteristica plus prominente in patientes con ulcerationes estatal. Le therapia de election esseva apparentemente reposo in lecto, elastic bandages supportative, e un essayo de injectiones de hexamethonium (bromido de bistrium). Sympathectomia lumbar pareva esser sin valor permanente.

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Myocarditis and Myocardosis

A Clinicopathologic Appraisal

By M. A. Blankenhorn, M.D., and Edward A. Gall, M.D.

Search of 3,141 autopsies found 108 examples of myocardial disease of which 77 were inflammatory (nonrheumatic) and 31 noninflammatory but degenerative and not due to sclerosis or hypertension. These are designated myocardosis. Myocarditis was associated with infections in a manner often described; myocardosis was associated with a variety of noninfectious disorders. A discussion of the use of this term is elaborated. Clinical records also were studied to find what part such lesions played in causing death and how such myocardial lesions could be diagnosed with more certainty.

A SIGNIFICANT renewal of clinical interest in myocarditis and other disorders of cardiac muscle has become manifest in recent years. Much of the impetus has stemmed from an increasing awareness that pathologists were frequently encountering intrinsic myocardial abnormalities in patients in whom these had been unsuspected during life. Also of contributory significance have been the growing use of the electrocardiograph and the development of therapeutic measures for the control of serious acute infections. The latter has led indirectly to the unmasking of evidences of myocardial dysfunctions previously considered manifestations of the underlying febrile disorder The combination of these factors has served to overcome a popular reluctance to consider myocardial disease a valid clinical entity.

The term "myocarditis" came into disfavor at the turn of the century; a reflection of its misuse as a basket category into which were placed sundry conditions for which no pertinent pathologic evidence was forthcoming.[1-3] The recognition in 1912 of the significance of coronary occlusion and its associated myocardial alterations all but eliminated primary disease of heart muscle from clinical teaching. Indeed, Sir Thomas Lewis sounded the prevailing note with the remark that the diagnosis "myocarditis" was not justified, save in relation to rheumatism and then "carditis" served a more representative purpose. On the other hand, Christian[1] (1950), among others, persisted in emphasizing the importance of primary myocardial disease in certain instances of heart failure. Confirmatory support for this stand has emerged during the past 10 years, in good part initiated by the large scale studies of Saphir (1941) and Gore (1947, 1948). Others have claimed an autopsy incidence as high as 10 to 15 per cent and have expressed the belief that most persons experience fleeting attacks of myocarditis in the course of various acute infectious disorders.[4, 5]

The present study was made to discover the incidence of myocarditis at autopsy in the Cincinnati General Hospital and further to evaluate the pathologic findings in relation to the clinical signs. An added purpose was the investigation of cases of "cardiac catastrophe," thus disclosed. A cardiac catastrophe is defined as a situation in which death resulted from myocardial insufficiency but in which this possibility was not recognized during life. It is not pertinent to this arbitrary definition that a correct diagnosis would necessarily have benefitted the patient. It is rather considered a catastrophe not to know what could have been known.

Material

The autopsy records of 3,141 cases examined during the five-year period, 1949 to 1953, were searched. Patients of all age groups were included. From this source were culled those cases with myocardial disease exclusive of that due to coronary artery insufficiency and rheumatic fever. There were no cases with diphtheritic heart disease in this period but there were 11 individuals with active rheumatic myocarditis.

From the Departments of Medicine and Pathology, University of Cincinnati and the Cincinnati General Hospital, Cincinnati, O.

The group thus gathered numbered 108 cases. Only routine sections of the heart were available for microscopic study and these ranged from two to eight per case, the average being three sections. Usually the right and left ventricles were represented. The lesions encountered were divisible into two major categories: Myocarditis, characterized by inflammatory exudates of varying intensity; and myocardosis in which cellular exudate was absent and the significant alterations were of retrograde or degenerative nature as defined in Dorland and used by American authors for a quarter of a century or more.[6-9] Seventy-seven cases comprised the myocarditis group and 31 cases were classified as myocardosis.

The clinical records in all of these cases were critically surveyed by one of us (M. A. B.), the autopsy findings were independently investigated by the other (E. A. G.). Each attempted, from the data available to him, to determine whether or not death was attributable to the myocardial disorder. A remarkable degree of conformity was attained on this score.

Pathologic Lesions

The lesions of myocarditis have as a common denominator the presence of a cellular exudate in the myocardium. Although Christian[10] pointed out that the suffix "itis" in a classical sense had little limiting connotation, it has become customary to utilize it as an indication of inflammation alone.[9] Unfortunately in the press of conservative interpretation of pathologic alteration of the myocardium, many have ignored the distinction between degeneration and inflammation. As a result such terms as toxic myocarditis and fibrous or fibroplastic myocarditis, intended to indicate noninflammatory lesions, have introduced a confusing note into the literature.[1, 2, 6, 7, 11-13] In our own studies we have held to the minimum requirement of inflammatory cell infiltration as a basis for the recognition of myocarditis. The character of the exudate was found to vary in respect to cell type, intensity and extent. No effort was made, however, to classify the lesion save to estimate whether it was of significance in contributing to the death of the patient. This was arrived at by evaluating both the myocardial process and the extracardiac findings disclosed by the autopsy.

In some of the cases, the lesions were widely distributed; in others, they were relatively spotty. In one instance coalescent, noncaseating tubercles of sarcoid constituted the outstanding feature. In most specimens the exudate was located in the interstitium, but replacement of myocardial fibers was also encountered. Varying degrees of muscle necrosis occurred. In view of Saphir's observation of a doubled yield in the incidence of myocarditis when 25 heart sections were prepared, it is assumed that a significant number of cases were missed in this investigation. Whether or not this error was of the order of 100 per cent, however, is open to considerable question. It is felt that relatively few cases in which the myocardial lesion actively contributed to death were not detected.

Myocardosis, a term coined by Riesman,[8] has not had wide usage in this country and is not remarked in most of the standard works in cardiology.[10] As a means of categorizing noninflammatory disorders of the myocardium and those degenerative conditions unrelated to coronary disease the term has found wider application in European publications.[11, 12, 14-16] Both clinical and experimental observations have justified the separation of these retrograde states from infectious and commonplace anoxic lesions.[17-26] In establishing a given alteration as a definitive lesion it is naturally necessary to avoid including banal postmortem changes. This has been done insofar as possible. Included as indicative of myocardosis have been such lesions as pronounced interstitial edema; swelling, lamination and proliferation of stroma; amyloidosis; shrinkage and irregularity or cloudy swelling, opacification, granulation and loss of striation of muscle fibers; hyalinization, over fragmentation; fatty degeneration and, in extreme instances, necrosis.[27]

Incidence

In the absence of a precise definition of myocarditis and a uniform method for histologic survey there is not much comparable meaning to the figures cited in the literature. Saphir[28] found myocarditis in 4.3 per cent of all autopsies at the Michael Reese Hospital (9 per cent when more elaborate methods were used), de la Chapelle[5] recorded 3.3 per cent at Bellevue

Hospital and Gore and Saphir[3] observed 3.5 per cent at the Army Institute of Pathology. This constitutes a surprising degree of agreement and our own figure of 3.4 per cent is quite in keeping.

Others, however, have claimed an incidence of 10 to 15 per cent.[3, 4, 6] On the other hand, there are many reports indicating a negligible appearance of myocarditis[29-31] in relatively large series of cases.

The different studies cited have had little uniformity in the types of cases excluded in arriving at a determination of the occurrence rate of myocarditis. Many have not considered newborn and stillborn cases, those dead on arrival, and those with valvular or coronary vascular disease. There has been much variation in the inclusion of cases with active rheumatic carditis and diphtheria. We have not considered it necessary to exclude any but the cases with rheumatic heart disease since it has not been possible in these to distinguish between death due to myocardial failure and that attributable to concomitant valvular distortion.

Clinical Studies

Viewed according to distribution of hospital services, the 108 cases were:

Service	*Myocarditis*	*Myocardosis*
Medical	55	24
Pediatrics	9	1
Surgical	7	3
Contagious	3	1
Dead on arrival	3	2

Myocarditis

In inflammatory myocarditis much has been made of the association of specific infections with myocarditis, this being the usual and sole proof of specific etiology. Saphir's major contribution was to show what specific infections were associated with, and hence etiologically related to, myocarditis in a vast number of situations. Following his technic, which is the simplest method available, we find much the same relations.

In 77 instances of inflammatory myocarditis there were 46 with recognized infectious disease:

13 found with pneumonia—lobar or lobular;
12 found with septicemia—not specified nor defined by cultures;
6 found with staphylococcal septicemia;
4 found with meningococcal septicemia;
3 found with virus diseases (2 polio, 1 neuronitis);
2 found with subacute bacterial endocarditis;
1 each with Friedlander pneumonia, tuberculosis, pyocyaneous infection, amebic abscess with secondary *E. coli* contamination, syphilitic aortitis, meningitis—organism not determined—and sarcoidosis.

As might be expected, the clinical picture of the patient found with myocarditis is dominated by systemic infections as shown above or by some associated organ system disease. The latter diseases are listed here in the order of frequency and are somewhat simplified for reporting:

Neurologic disorders (including cerebrovascular accident—many with associated pneumonia)	20
Malignant neoplasm (including lymphoma)	9
Acute and chronic lung disease	8
Trauma and poisoning	5
Diabetes	4
Kidney disease	3
Liver disease	3
Disseminated lupus	3
Necrotizing angiitis, periarteritis and hypersensitivity angiitis	3
Congenital heart disease	1
Peripheral vascular disease	1

Myocarditis was found to be accompanied by some other form of heart disease in 29 out of 79 instances. Listed in order of frequency were the following:

Acute endocarditis		8
Bacterial	6	
Nonbacterial	2	
Subacute bacterial endocarditis		3
Hypertensive heart disease		4
Chronic inactive valvular heart disease, rheumatic		3
Coronary artery disease		3
Pericarditis, acute		3
Cor pulmonale		2
Congenital		1
Syphilitic aortitis		1
Idiopathic hypertrophy		1

Electrocardiograms were not made on many of these 77 patients. In the 21 records available, the following abnormalities were reported

from interpretations done in the official cardiographic laboratory of the hospital:

Nonspecific myocardial abnormalities	11
Bundle branch block	2
Left ventricular strain	2
A-V heart block	1
Old myocardial infarct	1
Digitalis effect	1
Auricular flutter	1
Pericarditis suggested	1

One, only, was reported normal. In this latter instance cor pulmonale had been diagnosed and also chronic lung disease. The amount of myocarditis was not great.

In the 29 instances where other forms of heart disease were found present among the 77 cases of myocarditis, heart disease of some sort had been diagnosed clinically in 24, that is 24 of 29 patients, either previous to the final illness or in its course. The significance of such diagnosis is best comprehended by an opinion on whether myocarditis was the cause of death or contributed to death. This opinion was formed by each of the writers separately, as stated above. The clinical study was especially concerned to learn whether congestive failure was diagnosed, whether orthopnea, rapid pulse or low blood pressure was described and whether death was sudden. There was remarkably good agreement in the two separate opinions about the significance of the myocardial disease.

Among the 77 myocarditis cases heart disease was found to be the primary cause of death in 17, to be a contributing factor in 25, and to have no apparent relationship in 35 instances.

Among the 17 patients where myocarditis was the primary cause of death, five could be classed as cardiac catastrophies, as defined above. Essential details of these patients were briefly as follows:

Case 1, No. 160515, was a male, age 53. Cause of death was acute gastritis; heart failure. Heart disease was not diagnosed clinically although orthopnea, gallop rhythm with obscure heart sounds and dependent edema were found. No electrocardiograms were made. The heart weighed 570 Gm. and exhibited acute, severe myocarditis microscopically.

Case 2, No. 115839. Another such catastrophe was in a man of 65 who was being studied on the Surgical Service for a mass in the region of the liver. Heart disease was not diagnosed and no electrocardiograms were made, although there were obscure heart tones and orthopnea. There was evidence of nutritional failure and of peripheral neuropathy. The heart was described as grossly normal but the site of severe acute and chronic myocarditis. The abnormal mass proved to be a chronic amebic abscess. The patient had not received emetine.

Case 3, No. 267704, a male age 39, was in the hospital less than two hours, having collapsed while at work as a "helper around a bar". He was in circulatory collapse; heart disease was not diagnosed although there were obscure heart tones and orthopnea. He was considered to be ill with acute gastritis and nutritional cirrhosis, and no electrocardiograms were made. The heart was described as flabby, weighing 390 Gm. The cut section showed a striking mottled appearance. Microscopically there was hydropic degeneration of the myocardium thought to be indicative of beriberi heart disease. There was also, however, profuse diffuse infiltration of polynuclear leukocytes in interstitial spaces. The lesion was classified as acute myocarditis. There was nutritional cirrhosis and possible beriberi.

Case 4, No. 231080, a 28 year old male, was dead on arrival. At autopsy the heart weighed 445 Gm. and showed extensive severe infiltration with tubercles characteristic of sarcoid. There was similar involvement of lungs and liver but no evidence of congestive failure. He had been thoroughly studied on the Dermatological Service two years previously but no electrocardiograms were made and no heart disease diagnosed. It may be straining a point to class this as a catastrophe, but the patient was not followed in clinic nor advised about limitation of activity.

Case 5, No. 126799, a male 70 years old, was in the hospital less than 24 hours. Chronic lung disease and spontaneous pneumothorax were diagnosed. A tube thoracotomy was done and there was only transitory improvement. Heart disease was not diagnosed although there were obscure heart tones, orthopnea and edema. The electrocardiogram showed only atrial tachycardia. The heart was not grossly abnormal at necropsy. Atheromatous plaques were described in the coronary arteries. Microscopically there was severe subacute myocarditis.

Myocardosis

The 31 patients with myocardosis at autopsy were of about the same age and sex distribution as the 77 with myocarditis.

The association with infections is quite different, being almost with no relation, as follows: one with meningitis, one with pertussis, one or two with doubtful staphylococcal sepsis, also

postoperative sepsis. There were none with positive blood cultures—ante mortem or post mortem.

As to associated disease, the pattern is much the same as with myocarditis but with more of metabolic disorders than of infections. The associated diseases can be summarized somewhat loosely rather than clearly because several such associated diseases were coexistent and the relative value hard to define.

Pneumonia	5
Nutritional cirrhosis	5
Renal disease	4
Generalized arteriosclerosis	4
Renal disease	4
Lung disease	2
Poisoning (lye ingestion, CO)	2
Amyloidosis, secondary	2
Blood dyscrasias, agranulocytosis, thrombocytopenia	2
Obesity	2
Trauma	1
Periarteritis nodosa (not of heart)	1
Toxemia of pregnancy	1
Myxedema	1
Diabetes	1

There was relatively little associated heart disease of other category. There were two with hypertrophy and one with chronic valvular heart disease, probably sclerotic.

Electrocardiograms were made in 12 of these 31 patients. Eight were described as nonspecific changes, two with atrial fibrillation, one left ventricular strain and one sinus tachycardia. None was normal.

In this group heart disease was diagnosed 10 times during life. One, being suspected of hypokalemia, was treated with potassium chloride by mouth and later found with 12.8 mEq., but the cardiograms were not characteristic of potassium poisoning. Two with chronic renal disease had cardiograms not suggestive of potassium retention.

The significance of myocardosis in this group, as determined at autopsy and by clinical study, was: Primary cause of death, 10; secondary cause of death, 3; and no apparent relationship, 18.

There are six examples of cardiac catastrophe among these 29 patients with myocardosis.

Case 6, No. 261303, a female age 44, was known to be a chronic alcoholic and diagnosed as Wernicke's syndrome and nutritional cirrhosis, being in the hospital four days. No specific cardiac disorder was diagnosed although she was suspected of having mild congestive failure. The patient was examined by four physicians but no electrocardiograms were made. At autopsy the heart weighed 500 Gm. and was described as extremely flabby with pale brown myocardium. Microscopic study showed interstitial edema with vacuolization of muscle fibers considered consistent with beriberi heart disease.

Case 7, No. 280042, was a woman, age 52, with myxedema in whom heart disease was not diagnosed although there were obscure heart tones, orthopnea and edema. This patient was in the hospital but five hours and received no treatment. The heart weighed 400 Gm. and was not grossly abnormal except for considerable coronary sclerosis. Microscopic examination showed myocardial fibers widely separated by edematous interstitial tissue. Immediate cause of death was right heart failure.

Case 8, No. 19123, was a man of 49 with "chronic pneumonia" in whom heart disease was not diagnosed. Heart tones were obscure and gallop rhythm present. Electrocardiogram suggested right heart strain. Death was sudden and unexpected.

Case 9, No. 292482, a male age 81, was in a confused state but not with overt heart disease. Pleural fluid was found to contain type 3 pneumococcus. This later developed into frank empyema which was repeatedly tapped, being treated meanwhile with penicillin. The patient died suddenly immediately after a thoracentesis. The heart was not grossly abnormal but there was coronary sclerosis of considerable degree. Microscopic examination showed amyloidosis of the heart, widespread. Heart disease was not diagnosed clinically although there were obscure heart tones, gallop rhythm and orthopnea. Electrocardiograms showed sinus tachycardia and occasional ventricular premature contraction.

Case 10, No. 177767, was a woman of 35. Autopsy diagnosis was acute thrombocytopenic purpura and she was being treated for an obscure anemia with fever. She apparently had transfusion reaction but correct matching and grouping were reconfirmed. The myocardium showed extensive platelet thrombosis of capillaries. There were focal areas of necrosis and fibrosis and there was interstitial edema and fibrosis. Grossly the heart was normal. Electrocardiogram was normal. Pulse and blood pressure were not remarkable. No heart disease was diagnosed clinically although it is quite apparent that heart failure was the principal cause of death.

Case 11, No. 64569, was a woman, age 54, who died 15 minutes after being returned from the operating room where extensive surgery was done. She was described as "returned to the ward in good condition." When transferred from the cart to the

bed, she suddenly developed difficulty in breathing and the pulse was found slow and faint. She could not be revived. She had been ill over a year with rectal stricture and had been nine months with colostomy. Autopsy showed scanty findings. The heart weighed 375 Gm. with good coronary arteries and valves. Microscopic examination of the heart showed marked cloudy swelling and interstitial myocardial edema, slight myocardial fibrosis consistent with beriberi. Before operation systolic and diastolic murmurs had been described and the blood pressure was 170/100. No electrocardiograms were made. The final episode is typical of syncope reaction commonly seen in beriberi heart disease. It is suggested that the chronic gastroenteric disease was responsible for nutritional failure as shown in the myocardium.

Summary

A five year study at the Cincinnati General Hospital disclosed 108 cases of "myocarditis" in 3,141 autopsies from all services including newborn and stillborn and those dead on arrival; patients with rheumatic fever and diphtheria were excluded. This incidence, 3.4 per cent, is in keeping with reports from similar hospitals in New York and Chicago and from the Army Institute of Pathology.

In this study a distinction is made between inflammatory and degenerative myocardial disease, and the term myocardosis applied to the latter, of which there were 31 among the 108 total. A brief discussion of histologic criteria for diagnosis of myocardosis and somewhat about the history of this usage is given.

Inflammatory disease, i.e. myocarditis, was found associated with infections in much the same pattern as reported by others.

Myocardosis was usually unassociated with acute infections, but with a variety of intoxicants or metabolic diseases; prolonged pneumonia, nutritional type cirrhosis and renal disease were most frequent. Myocarditis was associated with other forms of heart disease in 29 of 77 instances. Myocardosis was seldom so associated. Electrocardiograms of both groups were abnormal with one exception and were interpreted variously—usually "nonspecific myocardial abnormality".

It was estimated that among the 77 patients with myocarditis, heart disease was the primary cause of death in 17, a contributing factor in 25, and unrelated in 35. Among 31 with myocardosis, heart disease was the primary cause of death in 10, a contributing factor in 3, and unrelated in 18. In the total series "cardiac catastrophe," i.e., where heart disease might have been diagnosed but was not, was found 11 times. Brief clinical notes about these are given, from which it is suggested that attention to certain physical signs might have led to diagnosis.

Summario in Interlingua

Un quintenne studio al Hospital General Cincinnati revelava 108 casos de "myocarditis" inter 3141 autopsias ab omne brancas de servicio, includente neonatos e mortenatos e personas morte al arrivar sed excludente casos de febre rheumatic e diphtheria. Iste proportion (3,4 pro cento) se trova de accordo con reportos ab simile hospitales in New York e Chicago e ab le Instituto de Pathologia del Armea Statounitese.

Nos distingue in nostre studio inter morbo myocardiac inflammatori e degenerative. Le typo degenerative, que nos designa como myocardosis, es representante per 31 in le total de 108 casos. Es presentate un breve discussion del criterios histologic applicabile al diagnose de myocardosis, insimul con alicun remarcas super le historia de iste termino.

Le morbo inflammatori, i.e. myocarditis, se trovava associate con infectiones in plus o minus le mesme maniera e al mesme grado como in le reportos de altere autores. Myocardosis esseva usualmente non-associate con infectiones acute sed con un varietate de intoxicantes o morbos metabolic. Le plus frequente inter istos esseva prolongate pneumonia, cirrhosis del typo nutritional, e morbo renal. Myocarditis esseva associate con altere formas de morbo cardiac in 29 inter 77 casos. Myocardosis rarmente monstrava un tal association. Electrocardiogrammas in ambe gruppos esseva anormal con un exception. Illos esseva interpretate in varie manieras, usualmente como "non-specific anormalitate myocardial."

Il es estimate que inter le 77 patientes con myocarditis, morbo cardiac esseva le causa primari del morte in 17 casos; illo esseva un factor contribuente in 25 casos; e illo habeva nihil a facer con le morte in 35 casos. Inter

31 patientes con myocardosis, le correspon-
ente numeros esseva 10, 3, e 18. "Catastrophe
ardiac"—i.e. morte in casos in que morbo
ardiac haberea essite diagnosticabile sed in
ue nulle tal diagnose esseva establite—oc-
urreva 11 vices in le serie total. Nos presenta
reve notas clinic in re iste casos e conclude
ue un plus alte grado de attention prestate a
erte signos physic haberea potite establir le
iagnose.

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The Serum Lipids in Human Atherosclerosis

An Interim Report

By J. C. Paterson, M.D., Betty R. Cornish, B.Sc., and E. C. Armstrong, M.D., C.M.

An attempt is being made to determine the relation of the serum lipids to the progression of human atherosclerosis. The serum lipids are estimated serially during life and are compared with the degree of atherosclerosis found post mortem. The findings in the first 50 fatalities in the series of 800 patients are reported. The results make a poor case for the effect of derangements of the serum lipids on the disease process. Elevation of the cholesterol-phospholipid ratio has the most suggestive atherogenic effect, but this is not consistent. The total serum cholesterol and the S_f 12–20 and 20–100 lipoproteins show no significant relationships.

RECENT observations in the field of lipid chemistry have suggested that derangements of some of the serum lipids may be responsible for the progression of the human atherosclerotic process. The derangements, most under suspicion at the moment, are (1) an elevation of the total serum cholesterol, (2) an increase in the serum cholesterol-phospholipid ratio and (3) an increase in the concentration of certain serum lipoprotein molecules, particularly those in the S_f 12–20 class.

Any or all of these derangements may well have a bearing on the pathogenesis of human atherosclerosis, but to establish this relationship is difficult. The stumbling block lies in the fact that the diagnosis of the disease, in its various degrees, is often impossible except on the autopsy table. The only reasonably reliable clinical manifestations are the signs and symptoms of coronary artery disease; but even here there are fallacies. It is fair to assume that patients with angina pectoris or demonstrable cardiac infarcts are probably suffering from a moderate or severe grade of atherosclerosis, but it does not follow that those without signs or symptoms (the so-called normal controls) do not harbor atherosclerosis of a similar degree. Asymptomatic coronary sclerosis is in fact extremely common. According to Page,[1] "Most investigators in the field of atherosclerosis quite confidently state that most adults have more or less of this condition. Yet these people with more or less atherosclerosis are the normal controls."

Thus, in order to establish a relationship between disorders of the serum lipids and an acceleration of the atherosclerotic process, a method more critical than clinical diagnosis is needed for the evaluation of the disease. We suggest that a more accurate procedure is to compare the degree of atherosclerosis seen *at autopsy* with the serum lipid picture, the latter being determined serially during life. Several points must be borne in mind in carrying out an assessment of this kind. Since atherosclerosis is a disease which may take years to develop and may persist for some time after the causative agent has ceased to act, the serial determinations of the serum lipids should be made over long periods.[2] Also, technics should be devised for measuring the degree of atherosclerosis at autopsy that are more accurate than the crude methods of morphological grading in general use today. And finally, allowances may have to be made for a possible regression of atherosclerosis, terminally, from wasting disease states.[3]

With these requirements in mind, we are presently assessing the importance of the serum lipids in the progression of atherosclerosis in approximately 800 patients who are permanently confined to our hospital. The serum lipid levels are being determined serially in these patients during life, and these antemortem findings are then compared with the mor-

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phologic grade of atherosclerosis and with the amount of lipid and calcium in arteries at death and autopsy. The present report will deal with the findings in the first 50 fatalities in the series. No conclusions will be drawn since the project is still in its infancy and we have not yet fulfilled completely the requirements given above for proper assessment.

Material and Method

The clinical material consists of 800 patients who are permanently confined to the hospital. In the series there are approximately 450 World War I veterans over 50 years of age who are confined with psychosis, approximately 250 World War II veterans under 50 years of age who also are confined with psychosis and 100 elderly World War I veterans who are in reasonably good health and are confined for domiciliary care.

We began our first survey of serum lipids in April, 1953. A second survey was carried out six months later and thereafter surveys were and will be made annually. At each survey, approximately 50 cc. of venous blood is withdrawn shortly after breakfast from each patient. After maximum clot retraction, the blood is centrifuged and the serum drawn off. A 10 cc. aliquot of each sample is placed in a serum bottle and shipped in wet ice by airmail for estimations of the S_f 0–12, 12–20, 20–100 and 100–400 classes of lipoproteins. These estimations are carried out soon after arrival of the specimen at the ultracentrifuge laboratory. This laboratory is maintained by the Department of Veterans' Affairs at the Department of Chemistry, McGill University, and is under the supervision of Dr. C. Winkler and Dr. R. F. Robertson.

The remainder of the serum sample is fast-frozen at −30 C. and stored at −18 C. until the patient dies and the postmortem examination is completed.* The serum is then removed from frozen storage, quickly thawed, and estimations of the free and combined cholesterol and the phospholipid are carried out immediately. The serum cholesterol is determined by the method of Schoenheimer and Sperry, as revised by Hawk and associates.[5] The phospholipid is determined by the method of Fiske and Subba Row, a modification of the Youngburg method, as given by Hawk and associates.[5] If two or more serum lipid estimations are carried out on a patient during life, the levels are averaged; (the maximum number of determinations on any one patient to date, June 1955, has been five).

When a patient dies and an autopsy is performed, the degree of atherosclerosis is evaluated in the abdominal aorta and the coronary, femoral and cerebral arteries, using six different indices of the severity of the disease: morphologic grading, measuring the thickness of the largest plaque, determining the total amount and concentration of lipid and of calcium deposited.

Morphologic grading is carried out on large segments of the four different arteries: the entire epicardial portions of the coronary arteries, the basilar artery and circle of Willis with approximately one half inch of each of their larger branches, the abdominal aorta extending from the lower border of the coeliac axis to the bifurcation, and the left femoral artery extending downward 12 inches from the inguinal ligament. These vessels are removed from the body, stripped of their outer medial and adventitial coats to remove contaminating fat (except for the cerebral arteries), and the degree of atherosclerosis is graded by a variety of criteria. The severity of disease in the coronary and cerebral arteries is evaluated, using the criteria of Davis and Klainer,[6] by which the degree of stenosis produced by the largest plaque is the critical feature. The severity of disease in the abdominal aorta is evaluated by other criteria, namely, the size of the largest plaque, the presence or absence of intimal erosion, mural thrombus or aneurysm formation and by the amount of calcification. The severity of disease in the left femoral artery is evaluated partly by the degree of stenosis produced by the largest plaque and partly by the same criteria that are used in the abdominal aorta. Once the morphologic grade of disease in each of the four arteries has been declared, a small segment of the largest plaque is removed, fixed in formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin. The thickness of the intima from the lining endothelium to the internal elastic lamina is measured with a micrometer eyepiece. The remainder of the material from each artery is submitted to the chemical laboratory for tissue analysis.

In the chemical laboratory, the fresh tissues are weighed at once and subjected to alkaline digestion and storage as recommended by Haven and associates.[7] After complete digestion an estimation of the total lipid content is made by the method of Haven and associates.[7] Another aliquot of the alkaline digest is subjected to acid digestion after the method of Ma and Zuazaga,[8] and the calcium content of this digest is estimated by the Clarke-Collip modification[5] of the Kramer-Tisdall method.

It must be stressed at this point that the morphologic grading (including micrometry), the antemortem serum lipid estimations and postmortem tissue analyses and the serum lipoprotein estimations are carried out independently by three distinct groups of workers. At no time is there collusion between members of these three groups; only when

* It has been shown in this laboratory by Cornish and co-workers,[4] that no significant deterioration of either serum cholesterol or phospholipid occurs for up to one year after fast-freezing and frozen storage.

TABLE 1.—*Age Distribution of the First Fifty Fatalities in the Series*

Age	No. of Cases
40 to 49 years	2
50 to 59 years	8
60 to 69 years	14
70 to 79 years	13
80 to 89 years	12
90 years and over	1

all estimations are completed are the final compilation of data and statistical analyses carried out.

The comparisons between the antemortem serum lipid levels and the postmortem morphologic and chemical findings are made by first segregating the postmortem data for individuals into three natural groupings. Thus, the series is divided into the three groups of morphologic gradings: severe, moderate and slight. And again, the series is divided into the three groups of lipid concentrations: highest, intermediate and lowest. A similar division is made for the other four indices. This division into groups is based on the natural range of levels for the number of cases available and is made without knowledge of the antemortem serum lipid picture. The next step is to eliminate the intermediate (or moderate) group and then to compare statistically the mean antemortem serum lipid levels of the remaining two groups by the method of Fisher.[9] Elimination of the intermediate groups is justified since the data for postmortem groups are arranged in order of increasing severity. P values of less than 0.05 are regarded as being significant, those equal to 0.05 are considered to be of borderline significance.

OBSERVATIONS

The age distribution for the entire series is given in table 1. It will be noted that almost all of the fatalities occurred in the sixth, seventh, eighth and ninth decades; a reflection of the fact that patients who are permanently confined to our hospital are older than those in most general hospitals. Unfortunately, the series does not allow at the moment an opportunity to determine the incidence of atherosclerosis or the character of the serum lipids in Canadian veterans. This opportunity may present itself, however, before the study is completed.

The primary diseases or states for which the 50 patients were permanently confined to hospital can be summarized as follows: schizophrenia, 12 cases; arteriosclerotic psychosis, 12 cases; syphilis of the central nervous system, 4 cases; senile psychosis, 3 cases; epilepsy with psychosis, 4 cases; other forms of psychosis, 11 cases; domiciliary care, 4 cases.

The immediate causes of death for these patients were: coronary artery disease, 15 cases; other sequelae of atherosclerosis, 3 cases; cancer, 12 cases; bronchopneumonia, 7 cases; miscellaneous conditions, 13 cases.

As mentioned before (Material and Method), the degree of atherosclerosis has been measured in autopsy material from the abdominal aorta and from large segments of the coronary, cerebral and femoral arteries in each of the 50 cases. The actual measurements were made in six different ways: by crude morphologic grading, by measuring the thickness of the largest plaque in each vessel, and by determining chemically the amount and concentration of lipid and of calcium in each vessel. After each of these postmortem measurements had been completed, the data were compared with the ante mortem serum lipid levels as described under Material and Method. Thus, an analysis has been made of the relationship of each of the six different measures of atherosclerosis, in four types of arteries, to the six different serum lipid levels, a total of 138 individual comparisons.*

Within these six analyses based on index of severity of disease only four of the 138 comparisons showed a significant relationship. In the analysis based on morphologic grading, three significant relationships occurred: an elevation of the cholesterol-phospholipid ratio and of the S_f 0–12 class of lipoproteins, both in cases with severe coronary sclerosis, and an elevation of the S_f 0–12 lipoproteins in cases with severe aortic sclerosis. In the analysis based on lipid concentration, the fourth significant relationship was found: an elevation of the cholesterol-phospholipid ratio in cases with severe femoral sclerosis. These two analyses are presented in tables 2 and 3.

* It has been impossible to assess the effect of the six serum lipids on the calcium concentration in the cerebral arteries. The quantity of this mineral was so small that when it was converted to a percentage the series could not be divided into three groups of concentrations.

TABLE 2.—*Comparison of the Morphologic Grade of Atherosclerosis with the Antemortem Serum Lipid Levels*

Grade of Sclerosis	Number of Cases	Cholesterol in mg.%	Chol. / P. Lipid Ratio	Lipoproteins in mg.%			
				S_f 0–12	S_f 12–20	S_f 20–100	S_f 100–400
Coronary Arteries							
Severe	22	246 ± 11*	1.04 ± 0.02	311 ± 15	45 ± 4	70 ± 6	21 ± 3
Moderate	20	235 ± 13	1.00 ± 0.03	289 ± 15	49 ± 5	75 ± 7	19 ± 3
Slight	8	219 ± 16	0.94 ± 0.03	237 ± 22	51 ± 9	88 ± 14	17 ± 4
Severe cf. slight *p* value.		>0.10	=0.01	<0.02	>0.10	>0.10	>0.10
Abdominal Aorta							
Severe	21	250 ± 48	1.03 ± 0.08	312 ± 13	50 ± 5	72 ± 6	21 ± 3
Moderate	19	234 ± 56	1.02 ± 0.13	283 ± 19	49 ± 5	85 ± 8	22 ± 4
Slight	10	216 ± 14	0.95 ± 0.03	258 ± 21	41 ± 6	62 ± 8	14 ± 5
Severe cf. slight *p* value.		>0.10	>0.10	<0.05	>0.10	>0.10	>0.10
Cerebral Arteries							
Severe	17	231 ± 14	1.03 ± 0.03	285 ± 18	47 ± 6	69 ± 5	15 ± 2
Moderate	17	237 ± 13	1.03 ± 0.03	294 ± 17	45 ± 4	69 ± 6	22 ± 4
Slight	16	242 ± 13	0.98 ± 0.03	293 ± 18	51 ± 6	88 ± 11	22 ± 5
Severe cf. slight *p* value.		>0.10	>0.10	>0.10	>0.10	>0.10	>0.10
Femoral Artery							
Severe	8	242 ± 21	1.04 ± 0.03	296 ± 28	41 ± 8	74 ± 8	23 ± 5
Moderate	25	246 ± 11	1.04 ± 0.02	309 ± 13	50 ± 5	74 ± 7	20 ± 3
Slight	17	221 ± 12	0.96 ± 0.03	260 ± 17	47 ± 4	76 ± 7	18 ± 3
Severe cf. slight *p* value.		>0.10	>0.05	>0.10	>0.10	>0.10	>0.10

* Mean ± standard error of the mean.

Limitations in space do not permit us to include the four other analyses (based on plaque thickness, total lipid, total calcium and calcium concentration) in which no relationships of even borderline significance occurred, nor the scatter diagrams which have been prepared for each of the individual comparisons based on quantitative measures of sclerosis. Inspection of the scatter diagrams gave no evidence of any further relationship than that obtained by comparison of the means of groups. Their analysis using the correlation technique was therefore considered unnecessary.

We are also presenting photographs of the abdominal aortas of 10 cases (fig. 1). These photographs show the five aortas (out of 50) with the least apparent degree of atherosclerosis and the five aortas with the most. The more important serum lipid levels for each of these 10 cases are also shown. It is obvious that these serum lipid levels are not related to the degree of sclerosis in these aortas.

The data presented in tables 2 and 3 are mean values of the entire series of 50 cases, not the data for individuals. Since some readers of this paper may be interested in this latter type of record we are giving in table 4 the data for each of the patients who died in the eighth decade. This series of 13 cases is too small for statistical analysis, but casual inspection shows: (1) There is no obvious relationship between the various serum lipid levels and the degree of atherosclerosis as measured in any of four different ways (we have omitted the data for

TABLE 3.—*Comparison of the Concentration of Lipid in Arteries with the Antemortem Serum Lipid Levels*

Lipid in mg. per 100 mg. Fresh Tissue	Number of Cases	Cholesterol in mg. %	Chol. / P. Lipid Ratio	Lipoproteins in mg.%			
				S_f 0–12	S_f 12–20	S_f 20–100	S_f 100–400
Coronary Arteries							
(a) 6.0 and over	12	236 ± 16*	1.03 ± 0.03	302 ± 22	40 ± 7	62 ± 7	23 ± 5
(b) 4.0 to 5.9	21	235 ± 13	0.99 ± 0.03	272 ± 17	49 ± 5	80 ± 6	19 ± 3
(c) Less than 4.0	17	238 ± 12	1.02 ± 0.03	299 ± 17	51 ± 5	78 ± 9	18 ± 3
Group (a) cf. group (c) *p* value		>0.10	>0.10	>0.10	>0.10	>0.10	>0.10
Abdominal Aorta							
(a) 8.0 and over	11	241 ± 15	1.01 ± 0.03	285 ± 22	54 ± 8	84 ± 12	22 ± 4
(b) 5.0 to 7.9	22	243 ± 12	1.03 ± 0.02	304 ± 14	47 ± 5	74 ± 7	20 ± 3
(c) Less than 5.0	17	227 ± 12	0.98 ± 0.03	275 ± 19	44 ± 4	71 ± 7	17 ± 3
Group (a) cf. group (c) *p* value		>0.10	>0.10	>0.10	>0.10	>0.10	>0.10
Cerebral Arteries							
(a) 4.0 and over	12	242 ± 13	1.03 ± 0.03	293 ± 23	55 ± 7	83 ± 5	22 ± 3
(b) 2.0 to 3.9	20	237 ± 13	1.01 ± 0.03	287 ± 15	47 ± 5	75 ± 8	17 ± 3
(c) Less than 2.0	17	231 ± 14	1.00 ± 0.03	288 ± 18	44 ± 4	72 ± 9	23 ± 3
Group (a) cf. group (c) *p* value		>0.10	>0.10	>0.10	>0.10	>0.10	>0.10
Femoral Artery							
(a) 3.0 and over	11	239 ± 9	1.06 ± 0.02	297 ± 15	39 ± 5	68 ± 5	21 ± 4
(b) 1.5 to 2.9	22	245 ± 14	1.02 ± 0.03	308 ± 16	50 ± 5	73 ± 7	20 ± 4
(c) Less than 1.5	17	226 ± 11	0.97 ± 0.02	263 ± 17	49 ± 5	82 ± 9	19 ± 3
Group (a) cf. group (c) *p* value		>0.10	=0.02	>0.10	>0.10	>0.10	>0.10

* Mean ± standard error of the mean.

total lipid and total calcium purely as a matter of convenience). (2) The severity of atherosclerosis, measured in several ways, varies rather widely in different arteries of the same individual. (3) Calcium deposition in the cerebral arteries is unusually slight compared with that in other arteries. The failure of atherosclerotic plaques in the cerebral arteries to calcify, even with severe grades of disease, has been noted previously by Buck and coworkers.[10] This has been confirmed in the present series and we intend to enlarge on this interesting finding at a later date.

One further point, one which is not disclosed in any of the data given above, deserves comment, namely, the variability in the levels of the serum lipids when they are measured serially during life over a period of from one to three years. The data have been analyzed in this respect and the results are summarized in table 5.

As shown in table 5, there was an excellent conformity in the serum cholesterol levels and in the cholesterol-phospholipid ratios when two or more determinations were available for each case. The S_f 0–12 lipoprotein class showed fairly good conformity; but the other classes of lipoproteins were extremely variable. The re-

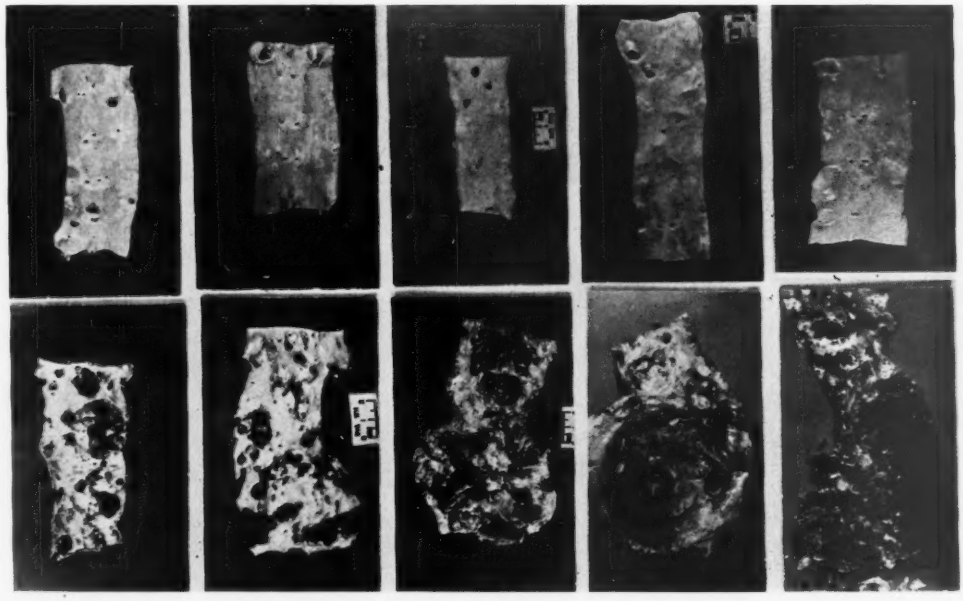
A – 68 – 53	
Age	74
Cholest.	247
C/P ratio	.91
S_f 12–20	54

A – 40 – 54	
Age	59
Cholest.	249
C/P ratio	0.89
S_f 12–20	68

A – 18 – 54	
Age	40
Cholest.	295
C/P ratio	1.14
S_f 12–20	44

A – 81 – 54	
Age	56
Cholest.	246
C/P ratio	0.97
S_f 12–20	36

A – 72 – 54	
Age	83
Cholest.	136
C/P ratio	0.90
S_f 12–20	21



A – 79 – 53	
Age	80
Cholest.	285
C/P ratio	1.13
S_f 12–20	63

A – 38 – 54	
Age	70
Cholest.	221
C/P ratio	1.08
S_f 12–20	29

A – 14 – 54	
Age	59
Cholest.	232
C/P ratio	1.05
S_f 12–20	42

A – 8 – 54	
Age	74
Cholest.	215
C/P ratio	1.07
S_f 12–20	22

A – 60 – 54	
Age	62
Cholest.	226
C/P ratio	0.96
S_f 12–20	49

FIG. 1. Ten of the 50 abdominal aortas in the series. The photographs in the upper row are from the five cases in the series with the least amount of sclerosis, while those in the lower row are from the five cases with the greatest amount. The antemortem serum lipid estimations are given for each case.

sults suggest that single determinations of serum cholesterol, cholesterol-phospholipid ratio and S_f 0–12 lipoproteins can be accepted as fairly reliable whereas single determinations of the other classes of lipoproteins cannot. An impression has also been gathered that extreme variations in the serum lipids occur in patients who are *in extremis*. If this is true, it throws some doubt on the validity of postmortem biochemical determinations of the serum lipids, a technic that has been used by others but not by us.

Finally, we have had the opportunity of comparing the levels of the serum lipids, examined during life, with the presence or absence of the usual sequelae of coronary atherosclerosis seen at autopsy: coronary thrombi, massive hematomata of the occlusive type, recent or old cardiac infarcts or sudden and unexpected death from coronary insufficiency in patients with severe grades of coronary sclerosis (and with no other apparent cause for sudden death). The results are given in table 6. It will be seen that there is no significant elevation of any of the serum lipid fractions in cases with those sequelae of coronary atherosclerosis which can be noted at autopsy, a result which conflicts with that obtained by others who have compared the serum lipids with the presence or absence of *clinical* signs of coronary artery disease.

TABLE 4.—*Postmortem Artery Findings and Antemortem Serum Lipid Levels in Fatalities in the Eighth Decade*

Autopsy Number	Age	Morphologic Grade				Plaque Thickness in microns				Lipid Concentration in mg./100 mg. Fresh tissue				Calcium Concentration in mg./100 mg. Fresh tissue				Serum Lipids in mg.%					
		Cor.	Aor.	Cer.	Fem.	Cor.	Aor.	Cer.	Fem.	Cor.	Aor.	Cer.	Fem.	Cor.	Aor.	Cer.	Fem.	Cholesterol	C/P ratio	S_f Lipoproteins			
																				0–12	12–20	20–100	100–400
A63-53	73	+	++	++	+	1050	1350	675	975	4.7	4.3	2.2	1.4	0.1	0.6	<0.1	0.7	190	0.94	195	28	75	18
A68-53	75	+	+	+	+	600	1425	750	2175	3.8	4.1	3.5	1.6	<0.1	0.5	<0.1	<0.1	247	0.91	289	54	95	9
A79-53	79	+++	+++	+	++	1200	3250	900	1350	3.3	6.7	2.4	3.7	1.0	4.8	<0.1	1.0	285	1.13	331	63	85	16
A91-53	70	+++	+++	+++	+++	1875	2250	975	1425	5.3	3.0	2.2	6.4	3.5	2.0	0.1	0.5	265	1.07	305	38	69	22
A111-53	74	+	+	+++	+	1050	4200	900	1425	4.4	7.3	4.9	2.6	0.2	0.5	<0.1	3.9	203	0.98	264	60	90	15
A15-54	73	++	++	+	+	1725	2325	375	375	3.3	2.8	2.0	1.0	0.1	0.3	0.1	2.0	183	0.84	245	56	126	21
A31-54	74	+++	+++	+++	+	1650	2475	825	1500	6.0	9.7	2.2	2.1	1.5	5.1	<0.1	1.6	243	0.97	280	48	51	26
A38-54	70	+++	+++	++	++	2100	1500	825	1125	8.0	7.9	0.7	3.1	2.1	0.5	1.7	0.3	221	1.08	272	29	57	17
A58-54	76	++	++	++	++	975	1200	75	750	1.4	8.2	0.6	1.5	0.8	1.8	0.9	2.3	309	1.23	358	72	123	53
A122-54	71	++	+	+++	++	1500	2100	1200	1425	3.7	5.0	3.6	3.1	0.8	1.1	<0.1	0.4	181	0.92	241	18	37	5
A123-54	71	+++	++	+++	+++	1950	1575	1500	2175	7.5	4.4	3.8	1.7	5.6	1.3	0.1	0.1	138	0.89	173	16	35	5
A3-55	79	++	+++	+	++	1500	2550	1050	2250	6.4	9.1	3.5	2.6	1.6	2.7	<0.1	1.8	192	0.95	277	18	23	5
A9-55	77	++	++	+++	++	525	1650	1275	375	4.6	6.3	8.7	1.6	2.7	2.3	<0.1	5.5	198	1.04	300	33	42	3

TABLE 5.—*Variability in Multiple Determinations of the Serum Lipid Levels*

	Cholesterol	C/P ratio	Lipoproteins			
			0–12	12–20	20–100	100–400
Mean Maximum %-Deviation	8.6	5.1	13.3	31.5	27.8	50.4
Percentage of cases with Mean Maximum %-Deviation of <15%..	81.6	100.0	61.5	33.3	33.3	10.3

DISCUSSION

First of all, it might be advisable to defend our use of psychotic patients in the present evaluation. An essential feature of our experimental procedure was that the patients be under control in hospital for long periods, and that, when they die, we could carry out a rather specialized type of pathologic examination. Inmates of psychiatric institutions would seem to fit these requirements best. However, it might be claimed that psychotic patients differ in many ways from members of the general population. In particular, it has been argued that they are prone to nutritional defects and metabolic derangements. These claims, of course, are true. We are even willing to concede that their serum lipid patterns may differ from those of nonpsychotic individuals. But our aim is not to study the mechanism of derangement of the serum lipids in psychotics; rather it is to evaluate the effect of these derangements, produced in any way, on the progression of atherosclerosis. We submit that the use of psychotics is just as valid in this respect as the use of diabetics. For those who are still sceptical, it should be mentioned that our series of 800 subjects includes 100 nonpsychotic subjects who are confined to the hospital for domiciliary care. Four of these have already died and they showed no difference in the general pattern from that shown in psychotics. We would stress also that almost all of the 46 psychotics in the present study were suffering from stages of psychosis that did not appreciably affect their physical health. They were ambulatory and fairly well nourished until the onset of their terminal illness.

It must also be admitted that there is no completely satisfactory way of assessing the severity of atherosclerosis in autopsy material.[11] Several methods have been suggested, including an estimate of the number and size of the lesions, a measurement of the thickness of the largest plaques, the amount and concentration of lipid and of calcium deposited in the arterial wall, the extent of atheromatous ulceration, and the degree of stenosis of the arterial lumen. Any one of these is far superior to clinical methods of assessment, but none is without error. For example: a solitary stenosing plaque in a small artery will have more effect on functional efficiency than many plaques of similar size in a larger vessel; the amount of lipid is not always increased in severe grades of the disease, the accelerating factor here being fibrosis rather than atheroma; the calcium deposition is sometimes just as much a result of aging as it is of progressive sclerosis; and necrosis with ulceration may destroy the apex of a large plaque, thus giving a fallacious result when the thickness of the plaque is measured. The situ-

TABLE 6.—*The Antemortem Serum Lipid Levels in Patients with and without Pathologic Evidence of Coronary Artery Disease*

	Number of Cases	Cholesterol in mg. %	Chol./P. Lipid Ratio	Lipoproteins in mg. %			
				S_f 0–12	S_f 12–20	S_f 20–100	S_f 100–400
Cases with lesions	20	247 ± 12*	1.05 ± 0.02	310 ± 17	49 ± 5	71 ± 7	21 ± 3
Cases without lesions	30	230 ± 10	0.98 ± 0.06	277 ± 12	47 ± 4	78 ± 6	19 ± 3
P value		>0.10	>0.10	>0.10	>0.10	>0.10	>0.10

Evidence of coronary artery disease was taken to be the presence of a coronary thrombus or other acute occluding lesion, a myocardial infarct, or sudden and unexpected death in individuals with severe coronary sclerosis (acute coronary insufficiency) without an acute occluding lesion or an infarct.

* Mean ± standard error of the mean.

ation being what it is, we have used as many indices of severity of disease as were practicable. Viewing and interpreting the results obtained in this way and not by any single method of analysis, a very poor case is made for the effect of the serum lipids on the progression of atherosclerosis: in only four out of 138 comparisons was a significant relationship apparent. The four exceptions, however, deserve some comment.

The diagnostic significance of an elevated cholesterol-phospholipid ratio in occult coronary artery disease has been suggested by Gertler and Garn.[12] It is also suggested by the experimental results of Duff and McMillan[13] and of Ladd and co-workers.[14] Our analysis, using morphologic grading as an index of severity of sclerosis, tends to confirm this relationship: although statistically significant in only one type of artery, the coronaries, the trend to an increasing antemortem cholesterol-phospholipid ratio with increasing severity of disease is evident in all four types of arteries (see table 2). Analyses based on the other five indices, however, give only one statistically significant correspondence between this ratio and a measure of severity of disease—in femoral arteries using lipid concentration as an index—and in none of these analyses is the trend in cholesterol-phospholipid ratios consistent in all four types of arteries. The picture, which we regard as an extremely interesting one, may be clarified when our series is extended.

The importance of the elevation of the S_f 0–12 class of lipoproteins, which was noted in two of our comparisons, is even more difficult to evaluate. This class of lipoproteins seems to be the one that is considered least significant either in experimental atherosclerosis or in the human disease evaluated by clinical methods. We are, therefore, inclined to view our two isolated significant relationships with some scepticism since they occur in only 2 out of 23 comparisons and since there is no indication of a consistent trend in all four types of arteries in any one analysis. One can be more dogmatic, however, regarding the S_f 12–20 and S_f 20–100 classes of lipoproteins. Neither of these showed any relationship to the degree of atherosclerosis in any artery, measured in any of six different ways. Their diagnostic importance for occult human atherosclerosis must therefore be taken as unproved in this preliminary series.

No conclusive information has been obtained regarding the possibility that aging or terminal loss in weight might invalidate the results of our various statistical analyses. It has been suggested, very properly, that an artery which has been exposed to the effects of an abnormal serum lipid level for 70 years will be more apt to show an acceleration of disease than one which is exposed to a similar abnormality for only 50 years. Accordingly, we have compared the severity of atherosclerosis in the four arteries, as measured in six different ways, with the ages of the 50 individuals in our series. In only seven, out of the 23 comparisons made in this way, was age significantly related to the progression of the disease. And it was noteworthy that the degree of atherosclerosis in the coronary arteries, measured in six ways, was not affected statistically by age. The artery that did show the greatest effect in this regard was the femoral (in four out of six comparisons).

Evidence of regression of the atherosclerotic process in terminal diseases of a wasting type was not conclusive in our series. Wilens[3] has stated that atherosclerosis is more severe in obese individuals than in those who are poorly nourished. It is therefore possible that absorption of the lipid in atherosclerotic plaques, with consequent reduction in the size of the plaques, might occur in the course of wasting diseases. The cachexia that results from cancer is an example of this theoretical effect. We have compared both the lipid concentration in the coronary arteries, and the morphological grade of coronary sclerosis, with the terminal change in body weight from the usual weight for each of the 50 cases. The results are given in tables 7 and 8. There may be some significance in the

TABLE 7.—*Comparison of the Lipid Concentration in the Coronary Arteries with the Terminal Change in Body Weight*

Lipid Concentration in mg./100 mg. Fresh Tissue	No. of Cases	Terminal Change in Weight (in lb.)
(a) 6.0 mg.% and over	12	-12 ± 6*
(b) 4.0 to 5.9 mg.%	21	-13 ± 4
(c) Less than 4.0 mg.%	17	-13 ± 5

Group (a) cf. group (c), p value = >0.10.
* Mean ± s.e.m.

TABLE 8.—*Comparison of the Morphologic Grade of Coronary Sclerosis with the Terminal Change in Body Weight*

Morphologic Grade of Sclerosis	No. of Cases	Terminal Weight Change (in lb)
a) Severe	22	-10 ± 3*
b) Moderate	20	-10 ± 5
c) Slight	8	-25 ± 7

Group (a) cf. group (c), p value = 0.05.
* Mean ± s.e.m.

relationship of terminal loss in weight to the morphologic grading of coronary sclerosis, but it is evident that terminal weight loss is not related to the concentration of lipid deposited in the coronary arteries.

There are still other reasons why we are not inclined to draw any conclusions from this preliminary survey. Our series is still small; we lack a satisfactory number of cases in the younger age group; only a few instances have been encountered in which there has been a gross disturbance in lipid metabolism; the serial determinations of the serum lipids have only been made over a 30 month period, far short of the time needed to eliminate the possibility of a metabolic upset that is no longer operative. Only time can correct these deficiencies. And in this regard we have tentatively (and perhaps optimistically) set a period of 10 years.

SUMMARY

An attempt has been made to determine the relationship between the levels of some of the serum lipids and the progression of the human atherosclerotic process. The serum lipids are estimated serially during life in 800 patients who are permanently confined to a hospital and the severity of atherosclerosis is evaluated when patients die and come to autopsy. To date, there have been 50 fatalities in the series.

The results of this preliminary evaluation make a very poor case for the effects of certain serum lipids on the progression of the disease. Elevations of the cholesterol-phospholipid ratio and the S_f 0–12 class of lipoproteins have been the only derangements that showed any suggestive atherogenic effects; but even these were not consistent. The other lipid fractions, notably the total serum cholesterol and the S_f 12–20 and the S_f 20–100 classes of lipoproteins, have not shown any significant relationships, when compared with the degree of atherosclerosis seen at autopsy. These latter findings contrast sharply with those of others who compared the serum lipid picture with the clinical signs of the disease. The project is continuing.

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SUMMARIO IN INTERLINGUA

Es interprendite le essayo de determinar le relation del lipidos seral al progresso de atherosclerosis human. Le lipidos seral es estimate serialmente durante le vita e es comparate con le grado de atherosclerosis constatate post morte. Es reportate le datos obtenite ab le prime 50 casos mortal in un serie de 800 patientes.

Le resultatos non representa un bon supporto pro le these que disrangiamento del lipidos seral affice le processo pathologic. Le elevation del proportion de cholesterol a phospholipido es le plus probabilemente interpretabile como apte a exercer un effecto atherogenic, sed isto non es uniforme. Le totales de cholesterol seral e le lipoproteinas Sf 12–20 e 20–100 non monstra interrelationes significative.

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Arteriosclerosis in the Intramural and Extramural Portions of Coronary Arteries in the Human Heart

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Fifteen instances of intramural coronary arteries were observed in the dissection of 276 human hearts at consecutive unselected autopsies. All but 2 of these 15 had severe atheromata and narrowing of the lumina. It was thought important to determine whether or not the covering of the artery by cardiac muscle for a major part of its course protected the artery from atherosclerosis. From our data, one may assume that those portions surrounded by heart muscle were not protected from atherosclerotic process which occurred there as well as in extramural portions of the same arteries and in other entirely extramural coronary arteries.

THE coronary arteries of the heart have been the subject of many thorough anatomic and physiologic studies. Numerous variations in the course of these vessels have been described. The coronary arteries usually course above the surface of the myocardium through the epicardial fat. Only at or near their termination do they dip into the muscle itself. In some patients, however, some of these arteries pass through the myocardium superficially and may be entirely surrounded by myocardial fibers soon after their origin; they may run in the muscle for the rest or main part of their course. Some arteries may dip beneath the myocardium for 1 to 3 cm. only to reappear on the surface for the remainder of their courses. Geiringer[1] could find little mention of this variation in the literature; he found no mention of its frequency nor a description of the state of the intima in such instances.

Geiringer studied the anterior descending branch of the left coronary artery because the straight course offered ease of measurement, and because atherosclerotic lesions appear early and are clinically important in this segment. The dipping into the myocardium is not necessarily confined to this vessel. He classified as mural those arteries in a narrow interventricular groove that had become folded over the artery with only a thin septum of connective tissue linking the periarterial space with the epicardium. He suggested that the artery, from a strictly anatomic sense, is epicardial, but, from a physiologic standpoint, intramuscular. He classified such arteries as mural in his report. Others were often completely surrounded by myocardium.

In 100 unselected autopsies at the Royal Infirmary, Edinburgh, the macroscopic incidence of mural type of left anterior descending coronary artery was 23. The distance the vessel was buried measured 5 mm. or more, at any part of its course. Microscopically, he found the covering fibers to be at right angles to the course of the vessel, the vortex fibers. He noted also that when full allowance was made for variation in age, sex, vessel size, heart weight, and especially the influence of hypertension, the mural portions of the left anterior descending branch tend to have a considerably narrower intima than the epicardial portions. "In other words, at the same age and sex, in hearts of the same weight, an epicardial left anterior descending artery of the same lumen as a corresponding mural branch, tends to have a considerably thicker intima." This fact was brought out by a study of microscopic slides in which a mural and an epicardial coronary co-existed. Geiringer states that it is quite

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TABLE 1.—*Location and Degree of Arteriosclerosis of Intramural and Extramural Segments*

Autopsy No.	Artery	Location of	Involvement	Degrees of	Involvement	Location of Intramural Segment	Length of Intramural Segment	Depth in Myocardium of Intramural Segment	Occlusion and Infarction
		Intramural	Extramural	Intramural	Extramural				
14967	LAD	2.5 cm. from origin of LAD	Middle of LAD	IV Calcified	IV	Prox.	0.5 cm.	0.6 cm.	Thrombus occluded LAD 1 cm. from orifice
14920	Rt. (predominant)	5 cm. from dist.	Middle and dist.	II	I	Mid.	2.0 cm.	0.3 cm.	None
14795	LAD	5 cm. from origin	Just prox. to intramural	IV Sclerotic prox. intramural	IV	Mid.	5.0 cm.	0.6 cm.	At intramural-extramural segment
14908	LAD	1.3 cm. from aortic origin	Dist.	IV Sclerotic	I. Distal 1 cm. fragments of thrombus	Entire artery	10.1 cm.	0.6 cm.	Recent thrombus distal portion of LAD. Intramural shows less arterioscl., but apex lt. ventricle shows areas of white fibrous tissue as does post. septum supplied by rt. coronary.
14852	LAD	1.3 cm. from origin	First 1 cm. was sclerotic	II	Proximal 1st 1 cm. sclerotic	Prox.	3.8 cm.	0.15 cm.	None
14850	Branch of LAD between LAD-Circumflex	2.5 cm. from origin	Dist.	I	I	Prox.	6.0 cm.	0.5 cm.	None
15438	LAD	1.3 cm. from origin	Middle and dist. LAD branch	IV Calcified sclerotic	III	Prox. and mid.	2.0 cm.	0.3 cm.	No occlusion but healed infarct post. wall lt. ventr. Recent infarct. ant. septum and ant. wall lt. ventr. with mural thrombus
15261	LAD	2.5 cm. from origin	Prox. and dist.	III	I	Mid.	1.3 cm.	0.15 cm.	None

15988	LAD	1st branch 0.5 cm. from ostium, branches 2 cm. from origin of 1st br.	I three fourths	IV	IV	Mid.	1.3 cm.	0.3 cm.	None
15862	LAD	2 cm. from ostium	Prox. 2 cm.	III	I	Mid. and dist.	7.5 cm.	0.6 cm.	None
15844	LAD	3 cm. from ostium	Thrombus at junction ē circumflex	IV Calc. with extensive atheromatosis in all intramural and beyond thrombus	IV	All dist. to 0.3 cm. from ostium	7.5 cm.	0.3 cm.	Thrombus in extramural segment at junction of LAD with circumflex branch
15817	Circumflex	4.5 cm. from ostium	Prox.	IV Calcified	I	Dist. half	All of distal half of artery	0.5 cm.	Prox. intramural part completely occluded by old thrombus
15565	LAD	2.5 cm. from ostium	Prox.	II	I	Mid. and dist.	4.0 cm.	0.6 cm.	None
15677	LAD	3.5 cm. from ostium	Prox. half	I	I	Dist. half	4.0 cm.	0.3 cm.	None
15618	LAD	2.5 cm. from ostium	Prox.	II	II	Mid. and dist.	5.0 cm.	0.3 cm.	None
15607	LAD	2.5 cm. from ostium	Prox.	II	II	Mid. and dist.	5.0 cm.	0.3 cm.	None

LAD = left anterior descending branch of coronary artery. Prox. = proximal. Dist. = distal. Mid. = middle.

TABLE 2.—*Clinical and Anatomic Data*

Autopsy No.	Age Sex Race	Diagnosis	Cause of Death	Wt. of Heart	Degree of Involvement
14967	74 F, W	EH, ASHD	Ac. myo. infarct.	380 Gm.	Gray thrombus 0.5 cm. from rt. cor. orifice, lt. circumfl. branch occluded by thromb. Adv. sclerosis desc. aorta, sl. of renal and splenic arts.
14920	69 M, W	Total gastrectomy for Ca	Postoperative.	470 Gm.	Moderate yellow plaques.
14795	68 F, W	Ess. hypertens.	Myo. infarct.	800 Gm.	Mkd. narrowing LAD, occlusion rt. cor., recent thrombus. Focal fibrosis and degen. of myo.
14908	62 M W	ASHD, BBB, EH	Rt. subdiaphragmatic abscess, fat necrosis pancreas after cholecystectomy.	510 Gm.	Arteriosclerotic narrowing, rt. coronary and gray thrombus partially recanalized 1.5 cm. from orifice.
14852	58 M, W	ASHD	EH cerebr. hemor., lt. cerebel. art.	710 Gm.	Rt. and lt. coronary arteries have plaques, entire course.
14850	71 F W	Arter. nephroscl., arterioscl., genl.	Myo. fail., pulmon. edema, angina pectoris.	700 Gm.	Mod. intimal plaques intramural branch LAD artery. Midway between LAD and circumflex free of sclerosis.
15438	72 M, W	ASHD	Ac. ant. myo. infarct.	420 Gm.	Abd. aorta has mural thromb. over plaque. Grade I sclerosis rt. cor.
15261	68 F, W	Hypertens. (malig.)	Mesenteric thrombosis infarct. 7′ of ileum.	330 Gm.	Adv. arterioscl. cor. art. with narrowed lumina. Focal fibrosis of myocard.
15988	48 M, W	Arterioscl., EH	Pulm. inf., heart fail.	575 Gm.	Mkd. arterioscl. cor. art., but no thrombosis.
15862	48 M, W	No HD	Bronchogenic Ca with metastases.	200 Gm.	Slight sclerosis coronary arteries. Small number raised plaques in aorta.
15844	78 M W	Ac. myo. infarct., chr. bronchitis, Ca hand.	Myo. infarct.	500 Gm.	Infarcts entire lt. ventr. wall & apex, involve. of septum; marked cor. art. sclerosis; thromb. junction of LAD and lt. circumfl. art.; rt. cor. art. & intramural portion markedly sclerotic.
15817	94 M W	Rt. hemiplegia., emphysema.	Old myo. infarct., bronchopneumonia.	330 Gm.	Adv. arterioscl. cor. art. & thrombosis of left circumflex, 4.5 cm. from origin; both intra- & extramural portions, adv. sclerosis.
15565	42 M, W	RhHD, mitral stenosis.	Congest. fail.	540 Gm.	Only a few atheromatous plaques.
15677	62 M, W	ASHD	Metastatic bronchogenic Ca	300 Gm.	Few plaques; no difference between intramural and extramural LAD.
15618	77 M, W	ASHD	Old thrombus rt. cor., recent basilar art.	340 Gm.	Adv. sclerosis all cor. art.; thick walls and calc. plaques.
15607	70 M, W	ASHD	Metastatic Ca rectum.	260 Gm.	A few elevated sclerotic plaques.

ASHD = arteriosclerotic heart disease.
BBB = bundle branch block.
Ca = carcinoma.
EH = essential hypertension
LAD = left anterior descending branch of coronary artery.
RhHD = rheumatic heart disease.

clear that mural stretches of the left anterior descending coronary branch are only rarely affected by atherosclerosis, in contradistinction to comparable epicardial segments where this is a common finding. He concluded that these mural vessels have a much thinner intima tha corresponding epicardial branches, the ex tremes of medial hypertrophy and atrophy ar found less frequently in them, and tha atheroma occurs only rarely in these mura

stretches. He reasoned that a media-like protective action of the surrounding myocardium occurred.

Methods and Results

It was because of our interest in such factors and the possible relation of local factors in the pathogenesis of atheromata and arteriosclerosis, that we investigated the subject. We carefully inspected a total of 276 hearts from unselected autopsies in the Barnes Hospital and St. Louis City Hospital. Arteries that merely dipped deep into myocardium at their terminal branches were not included. Three of the specimens had to be decalcified before sections could be made. There were 15 patients with intramural coronary arteries among 276 consecutive hearts examined post mortem, an incidence of 5.4 per cent. There were 13 left anterior descending coronary arteries, one right coronary artery, and one left circumflex coronary artery which were surrounded by myocardium for variable distances. In one instance, the right coronary artery had a main branch that ran intramurally. All other 14 intramural coronary arteries in the consecutive autopsies, and one (case 16) not in the consecutive group were major coronary arteries (table 1). Case 16 showed an intramural right coronary artery but it was found after examination of the consecutive group of 276 hearts and was not included for purposes of incidence.*

From the data in table 1 it is apparent that in the 16 hearts with intramural coronary arteries, there was appreciable thickness of the myocardium covering the artery, and not merely an invagination of epicardium or epimyocardium folded over the vessel. All but two of the intramural coronary arteries exhibited severe atheromata and narrowing of the lumen. The other extramural coronary arteries in these hearts showed atherosclerotic involvement also. Eight of the intramural coronary arteries had marked atherosclerotic involvement, six moderate, and two had slight changes.

The other extramural coronary arteries in each of the 16 hearts showed some atherosclerotic involvement also (table 2). None of the extramural arteries had complete absence of atherosclerotic changes. Eight of them had marked arteriosclerotic narrowing and four of these had thrombi occluding a portion of the vessel. Six of these extramural coronary arteries showed moderate, and two had slight arteriosclerotic changes. Hypertension was present in only two of the patients.

The sections of the extramural coronary arteries were examined with hematoxylin and eosin stain, with microincineration and elastic tissue stains. From our studies we conclude that the covering of a coronary artery by myocardium does not protect it from degenerative change. The same degenerative arteriosclerotic changes are found in the intramural portions of the major coronary arteries as are found in the extramural portions, and in other entirely extramural coronary arteries in the same, or in other hearts. There must be more than mechanical pressure exerted by systolic contractions of the myocardium, or the so-

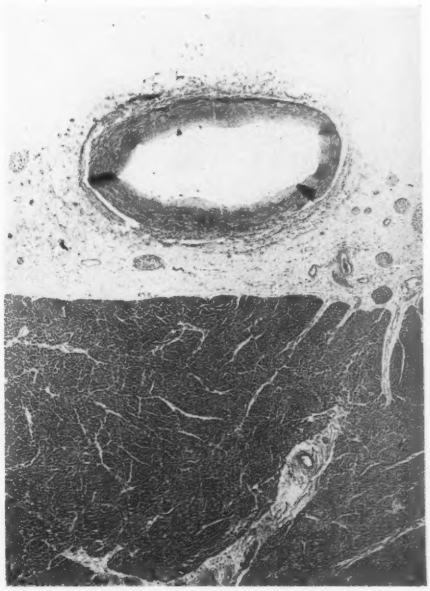

Fig. 1. A proximal segment of a major coronary artery in the epicardium showing slight intimal arteriosclerosis. All illustrations are from serial blocks of the same artery (× 35, hematoxylin-eosin stain). Figures 1, 2, 3 and 4 are all from case 15261, Barnes Hospital, St. Louis, Mo.

* At the request of the Editor the individual case reports are being omitted. These will be furnished on request.

FIG. 2. An intramural segment within 4 mm. from the section in figure 1, showing the artery completely surrounded by myocardium and involved by advanced arteriosclerosis (× 35, hematoxylin-eosin stain).

FIG. 3. A section from the adjacent block of the same intramural segment with only minimal evidence of arteriosclerosis. (× 35, hematoxylin-eosin stain).

FIG. 4. The distal segment of the artery after its return to an epicardial position. The vessel has branched and each branch is slightly arteriosclerotic (× 35, hematoxylin-eosin stain).

called protection from overdistention by the intravascular blood pressure involved in the process of atherosclerosis. That a single section of a coronary artery is not necessarily representative of the degree of arteriosclerosis in that artery or in other coronary arteries was illustrated in some of our sections (figs. 1, 2, 3 and 4) all of B. H., autopsy no. 15261. These specimens showed little arteriosclerosis, while sections 2 and 3 of the same short mural segment showed advanced changes. Sections (SE 795) of case 13 illustrate the importance of inspecting the coronary arteries thoroughly; a few sagittal cuts of a block of tissue taken at random when doing an autopsy are not sufficient. Certain areas of focal narrowing due to atherosclerosis would escape notice unless longitudinal cuts are made in the gross inspection, since it is not feasible to do serial sections microscopically. At least careful multiple sagittal cuts could be made, if preferred.

Microscopic Pathology. Hematoxylin and eosin stained sections of the principal coronary arteries of case 13, no. 14795 all show advanced arteriosclerosis with variable narrowing of the

lumina. There is a recent thrombus occluding the lumen of one of the sections of the right coronary. All sections of the principal coronary arteries show the vessels to be completely surrounded by epicardial fat. Special sections are taken of a smaller branch of one of the coronary arteries. There are three sections. One section shows the vessel in the epicardial fat; this section shows advanced arteriosclerosis. A second section shows one vessel to be partially but not completely surrounded by myocardium, and another vessel entirely in the epicardial fat. There is very little arteriosclerosis present in the vessel partially surrounded by myocardium, while the other vessel shows arteriosclerosis of an advanced degree with the lumen eccentrically narrowed by a plaque. A third section shows two small vessels of approximately the same size, both within the myocardium. One shows a large intimal plaque with an eccentrically narrowed lumen, while the other shows very little intimal proliferation. This last section, with the difference in degree of change in the two small vessels, is another illustration that intimal proliferation in arteriosclerosis is a focal lesion in many cases.

Summary

In a study of 276 human hearts to determine the incidence of intramural coronary arteries, with all or a major portion of a coronary artery covered entirely by myocardium, we found 15 such intramural arteries; an incidence of approximately 1 intramural coronary artery among every 23 examined. One additional heart with an intramural coronary artery was found but was not in the consecutive group of autopsies. In no instance was there more than one coronary artery intramural in any heart. All but two of the intramural coronary arteries exhibited severe atheromata and narrowing of the lumina. The other extramural coronary arteries in these hearts showed atherosclerotic involvement also. Eight of the intramural coronary arteries had marked atherosclerosis, six had moderate and two had slight atherosclerosis.

From the above findings one may assume that the covering of a coronary artery in the human heart by myocardium during a part of its major course fails to protect it from the atherosclerotic process which occurs there in much the same type and incidence as it does in the extramural portions of the same arteries and in other entirely extramural coronary arteries.

Acknowledgment

We are grateful to Dr. David M. Smith, Department of Pathology, Washington University School of Medicine (now at the University of Virginia) for his help in selecting the histologic sections used in making the figures.

We also wish to acknowledge the cooperation of R. A. Moore, M.D., formerly Professor of Pathology, Washington University Medical School, now Vice-Chancellor of the Schools of Health Professions, University of Pittsburgh, John Saxton, M.D., Pathologist at St. Louis City Hospital and wish to thank Ernest Booth, M.D., for supplying us with autopsy material for our investigation.

Summario in Interlingua

Esseva executate un studio de 276 cordes human con le objectivo de determinar le frequentia de arterias coronari intramural que es completemente o in major portiones coperite de myocardio. Dece-cinque tal arterias intramural esseva trovate. Isto es un frequentia de 1 arteria coronari intramural pro omne 23 casos examinate. Nulle del cordes examinate exhibiva plus que un intramural arteria coronari. Omne le arterias coronari intramural, con duo exceptiones, monstrava sever atheromas e reduction del passage. In iste cordes etiam le arterias coronari extramural monstrava un affection atherosclerotic. Octo del arterias coronari intramural exhibiva atherosclerosis a grado marcate, 6 a grado moderate, e 2 a grado leve.

Le supra-presentate constatationes permitte le conclusion que arterias coronari del corde human que es coperite in un portion major de lor curso per le myocardio non es protegite per ille copertura contra le processo atherosclerotic. Le processo atherosclerotic occurre sub le copertura in plus o minus le mesme maniera e con le mesme frequentia que in le portiones extramural del mesme arterias o que in altere arterias coronari cuje curso es integremente extramural.

REFERENCE

[1] Geiringer, E.: The relation of the mural coronary artery to arteriosclerosis. Am. Heart J. **41:** 359, 1951.

Studies on Water Excretion Following Intravenous Hydration and the Administration of Pitressin or Nicotine in Congestive Heart Failure

By Irwin B. Hanenson, M.D., Bernard Goluboff, M.D., Jacob Grossman, M.D., Raymond E. Weston, M.D., Ph.D., and Louis Leiter, M.D., Ph.D.

The diuretic response to intravenous infusions of 5 per cent glucose in water and the antidiuretic response to intravenous injections of nicotine salicylate and aqueous Pitressin, during maximal water diuresis, were studied in normal subjects and patients in congestive failure of varying severity. Patients in moderately severe congestive failure exhibited normal diuretic responses during the periods of intravenous hydration and normal antidiuretic responses following nicotine or Pitressin injections. Patients in more severe congestive failure failed to achieve comparable diuretic responses, following intravenous hydration; in the course of this, signs of increasing congestive failure developed, which were associated with further decrease in urine flows, at times, without any further decrease in renal hemodynamics. These studies confirm the impression that patients in moderate congestive failure have neither increased sensitivity to, nor reduced ability to, inactivate endogenous or exogenous antidiuretic hormone. In addition, the observation, that patients in more severe failure do not achieve adequate water diuresis during intravenous hydration, suggests that sustained production of antidiuretic production, independent of normal osmoreceptor control, may be contributing to their fluid retention.

EVIDENCE has accumulated that under certain circumstances in congestive failure mechanisms leading to the retention of water in excess of sodium may be activated. Metabolic studies from several laboratories[1, 2] have established that in cardiac patients the weight changes during the accumulation or removal of edema fluid are often greater than anticipated on the basis of the observed sodium balances. In addition, there have been reports that urine of edematous cardiac patients may contain increased amounts of antidiuretic material.[3, 4] More recently, it has been demonstrated that, in patients on low salt diets, retention of water without sodium, leading to increasing edema, hyponatremia and hypochloremia, may occur when chronic congestive failure is acutely intensified by the development of severe respiratory infection, digitalis toxicity or escape from adequate digitalization.[5] However, patients in congestive failure ordinarily can achieve water diuresis in response to intravenous hydration and exhibit no increased sensitivity to aqueous Pitressin.[6] Therefore, it was suggested that this water retention, occurring despite extracellular hypotonicity, may reflect sustained posterior pituitary antidiuretic hormone production,[5] presumably independent of osmoreceptor control and induced by the inadequacy of the cardiac output relative to the body's metabolic requirements.[5, 7-9]

The present study is a comparison of the diuretic and antidiuretic responses of subjects without heart disease and patients in congestive failure of varying severity, who were given intravenous water loads and, whenever feasible, intravenous injections of aqueous Pitressin and of nicotine salicylate, which is known to induce discharge of posterior pi

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Dr. Hanenson was a Rosenstock Memorial Foundation Fellow, 1951–1953.

uitary antidiuretic hormone.[10] The data permit evaluation of the response to exogenous nd endogenous antidiuretic material, and of he influence of the severity of congestive failre on water diuresis during intravenous ydration.

Methods and Materials

The 19 subjects of this study included 14 patients ith chronic rheumatic heart disease and five ithout heart disease. Seven of the patients (A. E., . McD., V. B., A. G., G. S., M. F., and K. S.) ere clinically classified as being in moderately evere failure. They could be maintained relatively omfortable and free of edema by bed rest, a sodium intake of 0.5 to 1.0 Gm., digitalis, and the periodic administration of mercurial diuretics. In contrast, six others (B. K., M. H., A. S., M. G., C. L. and E. R.), who responded only transiently to vigorous therapy and followed a progressively downhill course, were considered to be in severe congestive failure. One cardiac patient (G. G.), who had undergone mitral valve commissurotomy several months earlier for peripheral embolization, was maintained on digitalis, but exhibited no hemodynamic or clinical evidence of congestive failure. It should be noted that the cardiac patients were maintained on a low sodium diet, whereas the noncardiac subjects were on a regular diet.

Studies were performed with the patients semirecumbent and in the postabsorptive state. About one hour after administering approximately 600 ml. of water orally, a soft rubber, multi-holed, urethral catheter was inserted and an indwelling needle placed in the femoral artery. After control blood samples were withdrawn, induction of diuresis was attempted by giving a constant intravenous infusion* of 5 per cent glucose in water, generally containing sufficient potassium acetate or phosphate to maintain a slightly positive potassium balance. Except when urine flows exceeded 10 ml. per minute, urine collection periods, which varied in duration inversely with urine flow, were terminated by injections of sterile water and air into the bladder.

When urine flow reached fairly constant maximal values, a 0.3 milliunit per kilogram dose of aqueous Pitressin was given intravenously, and urine collections were continued until the flow returned to control levels. Then, nicotine salicylate was given intravenously in a dose of 2 to 6 mg. and the antidiuretic response followed as before. The higher doses of the alkaloid were given to smokers and to larger patients. In three patients (V. B., A. McD. and B. K.), the sequence was reversed, the nicotine being given first.

After completion of the water loading-Pitressin study, the clinical condition of several of the patients (G. S., A. G. and A. E.) interdicted the administration of nicotine. In five of the patients in severe congestive heart failure, neither drug was administered because adequate diuresis could not be achieved by intravenous hydration.

In some patients, inulin and para-aminohippurate clearances were measured throughout the studies. In others, the endogenous creatinine clearance was determined as an index of glomerular filtration rate.

Analyses of blood and urine samples were performed by methods described in previous publications from this laboratory.[11] Urine and serum total solute concentrations were measured by determining freezing point depression with a thermistor osmometer.*

Results

Response of Normal Subjects to Intravenous Water Loads and Pitressin

All five normal subjects, during hydration, reached maximal urine flows equal to or slightly greater than the infusion rate of 10 to 20 ml. per minute. Following Pitressin, the antidiuresis persisted for 40 to 60 minutes, reaching maximal flows of 1.2 to 5.7 ml. per minute (fig. 1). No consistent changes in electrolyte excretion or renal hemodynamics were observed, other than transient falls, attributed to "urinary tract dead space". Serum electrolyte concentrations varied in accord with the body fluid changes during hydration and antidiuresis (fig. 2).

Response of Patients in Moderately Severe Congestive Heart Failure to Intravenous Water Loads and Pitressin

In order to obviate untoward changes in circulatory dynamics, the patients in moderately severe congestive failure were given 5 per cent glucose infusions at rates which did not exceed 10 ml. per minute.

Five of the seven achieved maximal urine flows approximating the rate of infusion, whereas two (M. F. and A. E.) achieved maximal urine flows of only 6.8 and 8 ml. per minute, respectively (fig. 3). Following Pitressin, the flows fell to 0.7 to 2 ml. per minute, the antidiuresis persisting 50 to 70 minutes. One

* Constancy of infusion rate was maintained by use of a Bowman infusion pump.

* Manufactured by Fiske Associates, Boston, Mass.

subject (A. G.), after attaining a maximal flow of 10.4 ml. per minute, demonstrated a spontaneous fall to 5.7 ml. per minute, but subsequently responded like the others to Pitressin. The changes in renal hemodynamics and electrolyte excretion again reflected the influence of urinary tract "dead space" during periods of acute antidiuresis and diuresis (figs. 4 and 5).

One patient (B. K.) in severe failure, with intractable anasarca, achieved a maximal urine flow of only 4.7 ml. per minute after receiving a 5 per cent glucose in water infusion for 72 minutes at a rate of 5.7 ml. per minute (fig. 6). Although her serum osmolarity continued to fall, subsequently her urine flow gradually declined to 2.8 to 3.3 ml. per minute without sig-

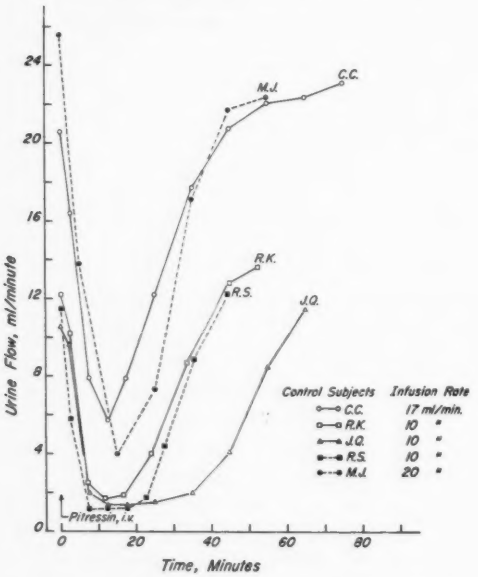

FIG. 1. The antidiuretic response of control subjects to the intravenous injection of 0.3 mU of aqueous Pitressin per kilogram of body weight, at the point of maximal diuresis during constant infusion of 5 per cent glucose in water solution. Note that zero time indicates the time of injection of aqueous Pitressin.

FIG. 2. The effects on urinary electrolyte and water excretion and renal hemodynamics, following intravenous injections of aqueous Pitressin and nicotine salicylate, in a typical control subject (R. S.), receiving a continuous infusion of 5 per cent glucose in water at the rate of 10 ml. per minute.

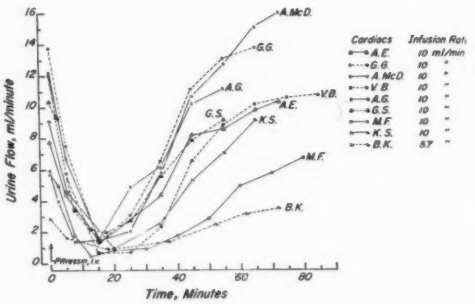

FIG. 3. The antidiuretic response of patients in moderately severe congestive failure to the intravenous injection of 0.3 mU of aqueous Pitressin per kilogram of body weight, at the point of maximal diuresis during constant infusion of 5 per cent glucose in water solution. Note that zero time indicates the time of injection of aqueous Pitressin.

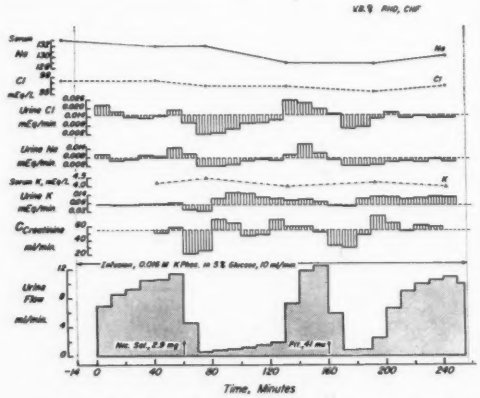

FIG. 4. The antidiuretic response of a patient in moderately severe congestive failure (V. B.) to intravenous injections of nicotine salicylate and aqueous Pitressin at the point of maximal diuresis during constant infusion of 5 per cent glucose in water solution.

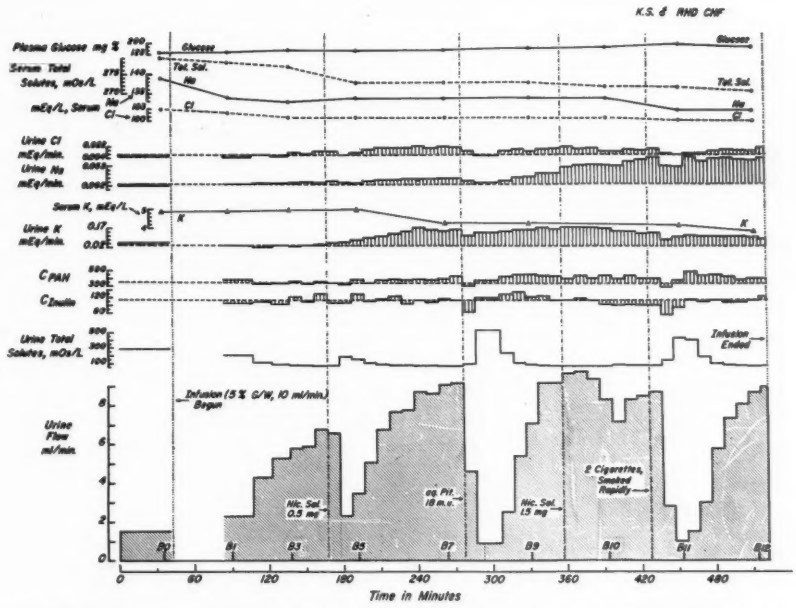

FIG. 5. The effects on urinary electrolyte and water excretion and urine and serum total solute concentrations, following intravenous injection of inactive solution of nicotine salicylate or aqueous Pitressin, and the rapid smoking of two cigarettes, in a patient in moderately severe congestive failure (K. S.), receiving a continuous infusion of 5 per cent glucose in water at the rate of 10 ml. per minute.

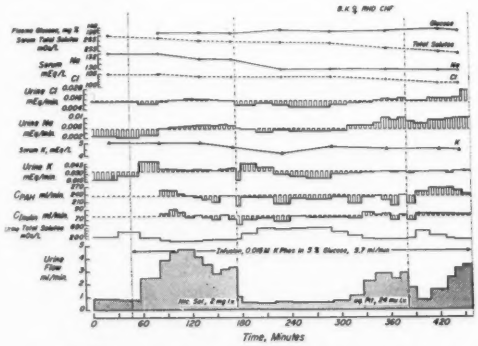

FIG. 6. The effects on urinary electrolyte and water excretions and serum and urine total solute concentrations following intravenous injections of nicotine salicylate and aqueous Pitressin, in a patient in moderately severe congestive failure (B. K.), receiving a continuous infusion of 5 per cent glucose in water at the rate of 5.7 ml. per minute.

nificant change in her inulin clearance. When given Pitressin following a partial recovery from a prolonged nicotine antidiuresis (167 minutes), her urine flow fell from 2.8 ml. per minute to 0.58 ml. per minute and within 67 minutes rose to 3.8 ml. per minute, at which time the infusion was discontinued.

Response of Normal Subjects and Patients in Moderate Congestive Heart Failure to Nicotine Administration during Intravenous Hydration

All five normal patients were given intravenous injections of nicotine salicylate. The resulting antidiuresis persisted for 50 to 100 minutes with minimal urine flows ranging from 0.7 to 2.9 ml. per minute (fig. 7) and bore no apparent relationship to the dose, even when this was corrected for body weight. However, it seemed to be increased in those patients who had severe and protracted reactions such as nausea, vomiting, dizziness, headache, paresthesia or local venous spasm.

In four of the six patients in moderately severe congestive failure (fig. 8), the nicotine antidiuresis was of equivalent intensity, but tended to be of somewhat longer duration than in the normal subjects. In one cardiac patient

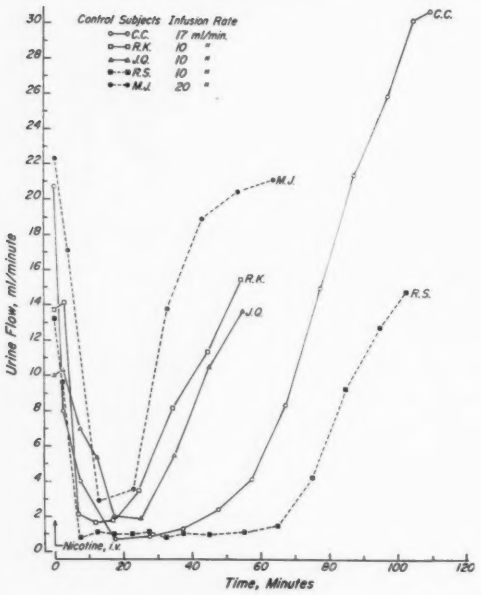

FIG. 7. The antidiuretic response of control subjects to the intravenous injection of nicotine salicylate at the point of maximal diuresis during constant infusion of a 5 per cent glucose in water solution. Note that zero time indicates the time of injection of nicotine salicylate.

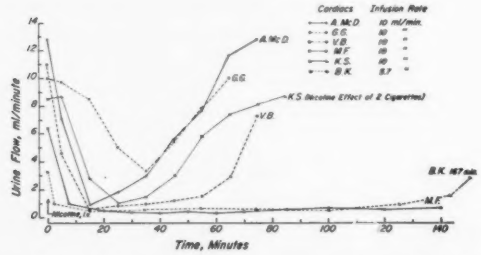

FIG. 8. The antidiuretic response of patients in moderately severe congestive failure to the intravenous injection of nicotine salicylate at the point of maximal diuresis during constant infusion of a 5 per cent glucose in water solution. Note that zero time indicates the time of injection of nicotine salicylate and that the antidiuretic effect in one patient (K. S.) is the result of the rapid smoking of two cigarettes.

(K. S.) the nicotine solution given was apparently inactive, for, after three ineffective injections, rapidly smoking two cigarettes brought about an antidiuresis which persisted for 70 minutes and reached a minimal flow of 1 ml. per minute. In one patient (M. F.), the antidiuresis persisted for three and one half hours, at which time the study was discontinued. During this part of the study, none of the normal subjects or patients had any significant changes in renal hemodynamics or electrolyte excretion (figs. 2, 4, 5, and 6), with the exception of C. C., a normal subject who had a transient rise in endogenous creatinine clearance with natriuresis and chloruresis following the nicotine antidiuresis.

Response of Patients in Severe Congestive Failure to Intravenous Water Loading

The diuretic response to intravenous infusions of 5 per cent glucose in water was also investigated in five patients who clinically were considered to be in more advanced congestive failure.

Patient M. H. was studied on three occasions, during the first two of which the infusion was administered at 10 ml. per minute. During the first procedure, her urine flow reached a peak of 1.4 ml. per minute, then gradually fell to 0.5 ml. per minute 80 minutes later as she developed increasing dyspnea, cough, neck vein congestion, tachycardia and other signs of congestive failure. Three weeks later, despite some clinical improvement, which was reflected by the rise in her serum sodium to 136 mEq. per liter and by her higher creatinine clearance, her urine flow achieved a maximum of only 2.1 ml. per minute, and declined as before with signs of increasing failure (fig. 9). This time, however, after discontinuing the infusion, she improved clinically and, subsequently, there was a gradual rise in urine flow to 5.2 ml. per minute, associated with an increase in creatinine clearance and urinary electrolyte excretion. In the third study, eight weeks later, the infusion rate was reduced to 5.7 ml. per minute because of the patient's low filtration rate. Again, the urine flow reached a maximal value of 1.5 ml per minute, and then fell. Clearances of inulin and para-aminohippurate (C_{IN} and C_{PAH}) (fig. 10) averaged 36.3 and 64.5 ml. per minute, respectively. No significant changes in electrolyte excretion occurred.

In patient C. L., who was given a 5 per cent

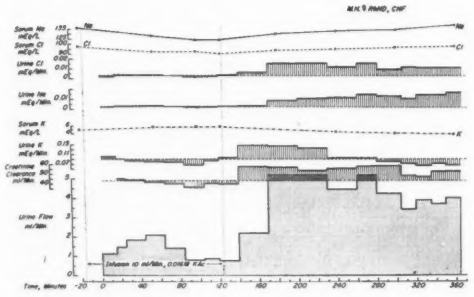

FIG. 9. The effect of infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute on serum electrolyte concentrations, urinary electrolyte and water excretion, and creatinine clearance during the second study on a patient in severe congestive failure (M. H.). Note the decrease in urine volume during the infusion, after achieving a maximal urine flow of only 2.1 ml. per minute, and the subsequent water diuresis following discontinuation of the infusion.

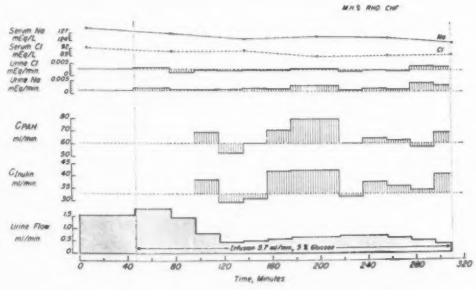

FIG. 10. The effect of infusing a 5 per cent glucose in water solution at the rate of 5.7 ml. per minute on serum electrolyte concentrations, urinary electrolyte and water excretion, and renal hemodynamics of patient M. H. in the third study. Note the progressive fall in urine flow during the infusion from the maximum of only 1.5 ml. per minute.

glucose in water infusion at the rate of 10 ml. per minute, although the serum sodium gradually fell from 126 to 114 mEq. per liter, the urine flow did not exceed 1.33 ml. per minute, and fell to a level of about 0.8 ml. per minute. Concurrently, his inulin clearance first fell from about 80 to 65 ml. per minute, and later rose, and his para-aminohippurate clearance fell from 234 to 149 ml. per minute and then rose slightly, filtration fraction increasing from 0.36 to 0.53. The very low urinary electrolyte excretions were not notably changed.

Patient A. S. had intractable anasarca and

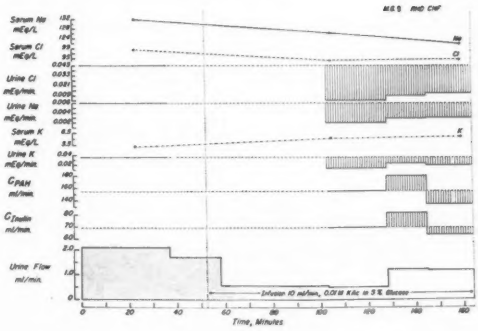

FIG. 11. The effect on serum electrolyte concentrations, urinary electrolyte and water excretion, and renal hemodynamics produced by infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute in a patient in severe congestive failure (M. G.).

serum sodium and chloride concentrations of 108 and 82 mEq. per liter, respectively. While receiving an infusion of 5.6 ml. per minute, his urine flow increased to 2.65 ml. per minute after 43 minutes, but, during the next 140 minutes, gradually declined to 0.65 ml. per minute, as signs of increasing failure developed. His inulin and para-aminohippurate clearances fell from 41.9 to 37.2 ml. per minute and 144 to 115 ml per minute, respectively. No changes in urinary electrolyte excretion occurred.

Patient M. G. was given the usual infusion at a rate of 9.2 ml. per minute (fig. 11). As the infusion was continued, her congestive failure increased and her urine flow diminished from a preinfusion maximum of 2.1 ml. per minute to 0.54 ml. per minute. Subsequently, although her serum sodium had fallen from 132 to 122 mEq. per liter, her urine flow increased to only 1.2 ml. per minute.

The final patient in this group (E. R.) had rapidly reaccumulating ascites and repeated episodes of hyponatremia due to water retention. After ingesting 600 ml. of water, her serum sodium and chloride concentrations were 113 and 81.9 mEq. per liter, respectively, her serum total solute concentration was 242 milliosmols per liter, and urine flow only 0.67 ml. per minute (fig. 12). During the 5 per cent glucose in water infusion at a rate of 5.7 ml. per minute for 186 minutes, her urine flow rose to a maximum of only 1.07 ml. per minute and

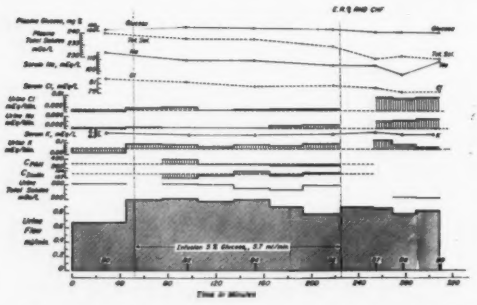

FIG. 12. The effect on serum electrolyte and total solute concentrations, urinary electrolyte and water excretion, urinary total solute concentration, and renal hemodynamics produced by infusing a 5 per cent glucose in water solution at a rate of 10 ml. per minute in a patient in severe congestive failure (E. R.).

gradually fell to 0.8 ml. per minute, as she developed symptoms of precordial constriction and signs of increasing congestive failure. Despite the fall in her serum sodium to 108 mEq. per liter, her inulin clearance remained between 126 and 132 ml. per minute and her para-aminohippurate clearance 270 and 303 ml. per minute with a filtration fraction of 0.44 to 0.46. Eighty minutes after the infusion was stopped her urine flow remained below 0.9 ml. per minute.

DISCUSSION

The present studies confirm the reported, essentially normal, response of patients in moderate congestive heart failure to intravenously administered Pitressin.[6] This suggests that such cardiac patients have neither increased sensitivity to, nor impaired ability to metabolize, presumably physiologic doses of an exogenous antidiuretic material. That both the osmoreceptor control of posterior pituitary antidiuretic hormone production and the metabolism of circulating antidiuretic hormone are also normal in these patients is suggested by the normal time required to achieve maximal urine volumes during infusion of isotonic glucose in water.

The attempt to compare the response of cardiac and noncardiac subjects to endogenous antidiuretic hormone released following nicotine salicylate was less successful. Although nicotine stimulates posterior pituitary release of antidiuretic hormone,[10, 12] the usual dose-response relationship has not been established. Identical doses, calculated on the basis of body weight or surface area, produce variable responses in different subjects, particularly in nonsmokers. All patients noted generalized tingling sensations, dizziness and some transient pain along the course of the veins of the injected arm, none of which appeared to influence the degree or duration of antidiuresis. Whenever the injections produced nausea and vomiting, antidiuresis was prolonged, as previously reported.[10] However, when the degree of antidiuresis following nicotine was comparable to that produced by Pitressin, as in patients A. McD., V. B. and K. S., the duration of antidiuresis was approximately the same. The analogous antidiuretic responses and patterns of recovery in these patients point to physiologic similarity or identity of endogenous antidiuretic hormone and Pitressin.

Evidence from several laboratories,[1-5] suggests that abnormal production of antidiuretic hormone, despite hypo-osmolarity of the body fluids, may contribute to the primary water retention in cardiac edema. That there may be some derangement in the metabolism of antidiuretic hormone in edematous patients with hepatic cirrhosis or nephrosis also has been suggested repeatedly.[13-15] The viewpoint that the underlying defect in hepatic disease was impaired ability of the damaged liver to inactivate the antidiuretic hormone[15] was apparently supported by the observations that extracts of normal rat liver inactivate Pitressin in vitro.[16] However, as in cardiacs in moderate congestive failure, both the maximal water diuresis during intravenous hydration and the antidiuretic response to physiological doses of aqueous Pitressin[17-19] or nicotine[19] were later found to be normal in cirrhotic patients.

In an earlier report,[5] it was suggested that continuing water retention need not require the large amounts of antidiuretic hormone in the serum sought by the proponents of the increased production theory. Such water retention may rather result from sustained or only slightly increased production of antidiuretic

hormone, in amounts not detectable by present methods and induced by mechanisms independent of control by the osmoreceptor system. Thus, in two of the five severely ill patients (M. H. and C. L.), infusing a 5 per cent glucose in water solution at a rate of 10 cc. per minute produced hypotonicity of the body fluids but resulted in only slight rise in urine flow, followed by spontaneous antidiuresis. In both patients, the increased antidiuresis was associated with evidence of increasing severity of congestive failure and slight, but continued, fall in filtration rate. The change in filtration rate was probably not the primary cause of the antidiuresis because similar patterns of decreasing urine flow have been observed without any significant change in inulin clearance (cf. patient E. R.).

Unless some unknown mechanism is causing water retention, such persistent or increasing oliguria, with increased urine/plasma ratios for total solute concentration, creatinine and inulin, but without significant change in filtration rate, suggests that there may be continued release of antidiuretic hormone despite the hypotonicity of the extracellular fluid. Spontaneous development of similar persistent antidiuresis has been observed in patients with acute intensification of chronic congestive failure. Only those therapeutic procedures which presumably either improved the cardiac output or diminished the abnormally high metabolic needs were found to result in water diuresis and re-establishment of more normal body fluid tonicity.[5]

Several investigators have advanced the concept that a common mechanism may be responsible for primary water retention in edematous patients with cardiac, hepatic or renal disease. Although some have suggested that the common denominator is a decrease in effective circulating volume,[20] others[5, 9] have felt that the change is not in blood volume per se but rather in the dynamics of the circulation. Although the receptors and effectors for this circulatory "homeostat" have not been delineated, evidence has been presented that the receptors may be situated in the cephalad portion of the systemic circulation,[21] the pulmonary circulation[22] or the arterial vascular tree.[23] This mechanism appears to affect excretion of both water and electrolytes in conditions as diverse as hemorrhage,[24] adrenal insufficiency, postural changes[25] or experimental expansion or contraction of total body fluid volume.[26]

In the present series of more severely ill cardiac patients, the intravenous water load not only failed to elicit normal water diuresis but, apparently, overburdened the already diminished cardiac reserve, leading to increasing severity of congestive failure. The decrease in renal plasma flow during the infusions may well be a reflection of the failure to maintain cardiac output, with consequent activation of the mechanisms described above, including augmented antidiuresis, although blood volume per se was probably increasing at the time.

It is not yet established what role the marked impairment of renal hemodynamics, and particularly the greater reduction in renal plasma flow than in glomerular filtration rate, may play in the impaired water excretion of patients in severe congestive failure. The increase in filtration fraction results in increased plasma protein concentration in the blood leaving the glomerulus to perfuse the peritubular capillaries. However, if the consequent rise in plasma oncotic pressure does influence tubular reabsorption, it should promote movement of not only peritubular fluid but also solute across the capillary membrane into the blood. This purely physical process may be augmented also by the marked slowing of renal blood flow, which prolongs the time available for osmotic equilibration.

In addition, the reduction in filtration rate, which decreases the load of both electrolyte and fluid delivered to the distal renal segments, might be expected to increase the final concentration gradient produced by a given level of circulating antidiuretic hormone. However, it has been recently reported that acute unilateral reduction in glomerular filtration rate in dogs does not result in an increased urine/plasma total solute ratio.[28] Unfortunately, the filtration fraction in these experiments decreased.

Although the hypothesis of sustained antidiuretic hormone production is attractive, it

must be emphasized that these studies could not determine definitively whether impaired inactivation of circulating antidiuretic hormone and/or other mechanisms may not also be involved in the unsatisfactory diuresis of patients in very severe congestive failure. However, following oral water administration or after discontinuance of the intravenous hydration, all five were able, finally, to increase their urinary water excretion, presumably by inhibiting antidiuretic hormone production and inactivating circulating antidiuretic hormone. Moreover, cardiac patients in equally severe congestive failure exhibited neither increased sensitivity to, nor impaired ability to inactivate Pitressin tannate in oil given intramuscularly.[27] Therefore, their primary water retention may represent sustained or increased antidiuretic hormone production secondary to intensification of congestive failure.

Summary

Seven cardiac patients in moderately severe congestive failure achieved urine flows of 6.8 to 14 ml. per minute during constant intravenous infusions of 5 per cent glucose in water at rates of 10 ml. per minute. One cardiac subject with intractable anasarca achieved a maximum urine flow of 4.7 ml. per minute during a similar infusion at a rate of 5.7 ml. per minute. All eight patients gave an antidiuretic response to intravenous injections of 0.3 mU of aqueous Pitressin solution per kilogram of body weight, which was equivalent in degree and duration to that given by five normal subjects.

The antidiuretic response of four of five cardiac patients in moderately severe congestive failure to intravenous injections of 1 to 3 mg. of nicotine salicylate was also equivalent in degree and duration to that of five normal subjects. The antidiuretic response of the fifth cardiac persisted throughout the 205 minutes of observation following the nicotine injection. After rapidly smoking two cigarettes, a sixth cardiac patient gave an antidiuretic response which was equivalent to that of normal subjects given nicotine injections.

Five patients in more severe congestive failure, when given intravenous infusions of 5 per cent glucose in water solutions at rates of 5.7 or 10 ml. per minute, achieved maximal urine flows of only 1.1 to 2.7 ml. per minute. As the infusions were continued, signs of increasing congestive failure developed and, despite the continued fall in serum sodium and total solute concentrations, their urinary flows decreased to 0.4 to 1.2 ml. per minute, at times, without any further change in renal hemodynamics.

These studies support the view that patients in congestive failure of moderate severity have neither increased renal tubular sensitivity to, nor decreased capacity to inactivate antidiuretic hormone of endogenous or exogenous origin. The inability of the patients in more severe congestive failure to achieve satisfactory water diuresis during intravenous hydration suggests that one of the mechanisms contributing to their salt and water retention may be sustained production of antidiuretic hormone, which is independent of osmoreceptor control.

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Summario in Interlingua

Iste studios supporta le conception que patientes in disfallimento congestive de grado moderate ha ni un augmentate sensibilitate reno-tubular a hormones antidiuretic de origine endogene o exogene, ni un reducite capacitate a inactivar tal hormones. Le incapacitate del patientes con plus sever disfallimento congestive a attinger un forma satisfacente del diurese de aqua pare indicar que un del mechanismos contribuente a lor retention de sal e aqua es possibilemente le production sustenite de hormon antidiuretic, lo que es independente del regulation osmoreceptori.

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The Calibration of Heart Sound Intensity

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There is no standardized method for the calibration of total energy conducted to the surface of the chest caused by the cardiac sounds. Loudness is a subjective term which is dependent upon total energy, frequency of the main components and the specific sensitivity of the human hearing mechanism. A method is described in which the amplitude of the chief component of the heart sounds is compared to that produced by a standard sound signal at 80 decibels at 500 cycles per second and an intensity ratio calculated. The method has been applied to normal individuals of different ages and to those with mitral valve disease and those with pulmonary hypertension. The findings confirm the clinical observation that mitral stenosis with persisting mobility of the valve leaflets is associated with a loud first heart sound. However, the measurement of intensity of the second heart sound did not show so reliable a correlation between the loudness of the sound and the pulmonary blood pressure. The relationship is somewhat obscured by the wide range of normal values in the intensity of the second heart sound.

THE clinical subjective assessment of the intensity of heart sounds is generally accepted as valuable, but few attempts at objective calibration have been made. Since heart sounds consist of superimposed vibrations of various frequencies and intensities, most workers have approached the problem by separating the various components of a sound into frequency bands by means of filters[1-3, 8] and comparing the signal thus received with a signal of known frequency and energy.[1-3] By this means, the intensity of each frequency band can be recorded in absolute units of energy. While the intrinsic value of this procedure may be considerable, the technic is too complicated for widespread clinical application and the results are not easy to correlate with the subjective impression of loudness.

An alternative approach would be to employ a microphone constructed to attenuate low frequency vibrations to the same extent as the average human ear[4] and to compare the resultant heart sound deflections with those produced by a standard sound signal. Methods for the registration of a standard sound signal have been reported by Wells and co-workers in 1949[5] and Sloan and Greer in 1955.[11] There is obviously some variation in the audiograms of different individuals so that no microphone can be constructed with response characteristics which will exactly reproduce the auditory impression of each individual physician. However a microphone constructed to the "average audiogram" will produce deflections which are closely comparable to the impression of loudness obtained on auscultation by all with normal hearing. This method of calibrating heart sounds would not give a result in terms of absolute units of intensity. It would rather supply a method of measuring the intensity of sound phenomena in an arbitrary unit, thus enabling comparison of all records obtained by instruments which have the same frequency response characteristics, a chest piece of the same size and shape, and the same standard sound signal. So far as we are aware, no clinical application of this method of calibration has been made.

The intensity of the first and second heart sounds of a series of normal and abnormal cases was measured, and the method was found to be both practical and valuable in interpretation of records. Because of variations in the phonocardiographs in general use, however, these results are only applicable to a limited number of centers using identical equipment. This report is made in the hope that it will stimulate

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measures to secure some standardization in the manufacture of phonocardiographs for clinical use.

Method

"Logarithmic recordings" were made with a Sanborn Tribeam Stethocardiette while the patient was at rest in the supine position. To minimize the attenuation due to pressure of the chest piece on the skin, a large open bell of 4 cm. diameter was applied with the minimum amount of pressure necessary to produce skin contact over the whole diameter of the bell.[4, 6] A standard sound signal (80 decibels at 500 cycles per second) was recorded after each tracing at the same intensity setting of the instrument, as described by Wells and associates.[5] The maximum deflection produced by a heart sound divided by the deflection produced by the standard signal gave a value which will be referred to as the intensity ratio (I.R.).

The normal variability of the first sound was ascertained by measuring the intensity ratio from apical records of 67 subjects without cardiovascular or respiratory disease. Comparison was made with two abnormal groups (table 1). The first consisted of 34 asymptomatic individuals with "mild or doubtful mitral valve disease," who had previously had rheumatic fever and who showed evidence of mild or minimum cardiac involvement. The only evidence of cardiac involvement was a soft basal diastolic murmur in four cases, an apical systolic murmur in seven, and a systolic murmur and faint or doubtful mid-diastolic in five. In the remainder, apical mid-diastolic murmurs of more than grade 1 intensity were heard and recorded. The second group with which comparison of the first sound was made consisted of 44 patients with well developed mitral valve disease and varying but definite disability. Of these, 39 were thought to have moderate or severe stenosis, and five to have predominant regurgitation.

The normal variability of the second sound was estimated from records obtained in the pulmonary area from 63 subjects in whom there was no evidence of, or cause to suspect, pulmonary hypertension, abnormality of the semilunar valves, or chest disease, and was compared with the second sound of 27 subjects with pulmonary hypertension (table 2) proved by cardiac catheterization.

Table 1.—*The Age and Sex Distribution of 145 Subjects in whom the Intensity of the Apical First Sound was Measured*

	Cases	Sex		Age	
		M	F	Mean	Range
Normal	67	35	32	30	9–76
Mild or doubtful M.V.D.	34	11	23	26	9–58
Well developed M.V.D.	44	15	29	38	12–89

M.V.D. = Mitral Valve Disease.

Table 2.—*The Age and Sex Distribution of 90 Subjects in whom the Intensity of the Second Sound Was Measured*

	Cases	Sex		Age	
		M	F	Mean	Range
Normal	63	23	40	24	9–58
Pulmonary hypertension	27	14	13	34	11–60

Results

The mean intensity ratio (I.R.) of the first sound of normal subjects (after excluding one case with a P-R interval of less than 0.13 second) was 4.2 (standard deviation 2.6). Comparison of males and females of equivalent ages showed no significant difference while analysis by age groups suggested slightly higher values in the younger ranges (table 3). For the purpose of this study, an intensity ratio of 9.4 was considered to be the upper limit of normality (mean + 2 S.D.).

The first sound of 44 cases of well developed mitral valve disease exceeded this limit in 39 instances (fig. 1), all of which, except one, represented cases of significant stenosis. This exception was considered on clinical grounds to have predominant regurgitation. Of the five with normal intensity ratios, one presented as predominant stenosis (with calcification of the mitral valve), one was found at autopsy to have pure mitral regurgitation, one was found at surgery to have predominant regurgi-

Table 3.—*The Intensity Ratio of the First Sound in Normal Subjects Divided into Age Groups*

Subjects	Age (yrs.)	Intensity Ratio	
		Mean	S.D.
10	9–19	6.3	3.3
30	20–29	4.2	2.2
11	30–39	3.3	2.5
16	40–76	3.4	3.5
67	9–76	4.2	2.6

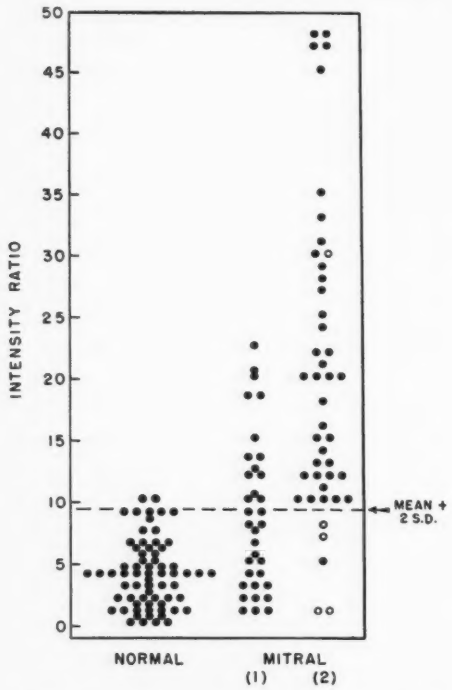

FIG. 1. The intensity ratio of the apical first sound of normal subjects, subjects with mild or doubtful mitral disease (column 1), and subjects with well developed mitral disease (column 2). Open circles represent cases with predominant mitral regurgitation.

tation, and in the remaining two, clinical evidence of combined regurgitation and stenosis was strong.

The intensity ratio of the first sound in the 34 cases of mild or doubtful mitral valve disease was above normal in 14 instances. Of these, in only nine, could an apical diastolic murmur be heard or recorded phonocardiographically, and in one a basal diastolic murmur was the only evidence of rheumatic involvement.

The correlation between high intensity ratio and clinical assessment of loudness was moderately good. Of those first sounds with an abnormally large intensity ratio, 79 per cent were reported as clinically loud, and of those with an intensity ratio within normal limits, 89 per cent were judged to be normal or reduced on auscultation.

The mean intensity ratio of the pulmonary second sound in the 63 cases without pulmonary hypertension was 5.9 and the standard deviation, 4.5. This extremely wide scatter was partly due to the fact that the intensity of the second sound apparently diminished

TABLE 4.—*The Intensity Ratio of the Second Sound in "Normal" Subjects Divided into Age Groups*

Subjects	Age (yrs.)	Intensity Ratio	
		Mean	S.D.
14	9–19	8.6	7.2
36	20–29	5.9	5.0
13	30–58	2.7	1.8
63	9–58	5.9	4.5

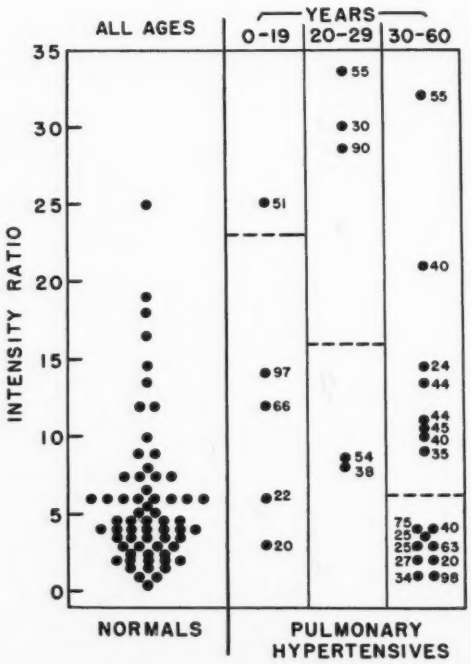

FIG. 2. Comparison of the intensity ratio of the second sound in the pulmonic area in normal and pulmonary hypertensive subjects. The pulmonary hypertensive subjects in the three right hand columns are divided into age groups. The mean pulmonary artery pressure at cardiac catheterization is represented with each case. The horizontal intermittent lines represent the upper limit of normality (mean plus twice standard deviation) for each age group.

strikingly with increasing age (table 4). No difference was apparent between the two sexes. Although the limits of normality could not be accurately assessed without a larger normal series of more representative ages, a rough approximation could be made for age groups 0 to 19 years, 20 to 29 years and 30 to 60 years (table 4). Using the values of the mean plus twice the standard deviation as the upper limit of normal, 12 of the 44 pulmonary hypertensive subjects had abnormally loud second heart sounds in the pulmonary area. It is evident from figure 2, in which the mean pulmonary artery pressure at cardiac catheterization is represented against each plot of intensity ratio, that the latter measurement is of relatively little value in determining the presence and degree of pulmonary hypertension.

Discussion

Anatomic differences, such as chest wall thickness, influence the intensity of the heart sounds recorded on the surface to a large extent and, as has been pointed out by Luisada and Gamna,[7] the standardization signal should be made ideally to arise within the heart. In this manner the true intensity of heart sounds could be estimated. However, this is impracticable, and it would seem that the application of a standard signal to the left anterior axillary line as practiced by these workers is no solution. As demonstrated by their results, the facility with which sound is transmitted from the axilla to a microphone at the apex is not always an index of its transmission from the heart to the apex. Therefore, the method described above does no more than quantitate the intensity of sound received at the surface of the chest without attempting to ascertain the intensity generated in the heart.

"Logarithmic" recordings attenuate low frequency vibrations in a similar fashion to the human hearing mechanism[4, 6] so that heart sounds are registered as they are perceived on auscultation. An abnormally high intensity ratio may consequently be the result either of abnormally large vibrations of low intensity or of unusually high frequency components or both. The loud first sound of mitral stenosis appears to be due to both these factors[8] and, in fact, the presence of high frequency components is perceived by the ear as a "sharp" or "ringing" or "snapping" quality.

The fact that there was not an even closer correlation between subjective impressions of loudness and the intensity as measured in this manner may be due partly to observer error. However, two other reasons for a discrepancy exist. One is the fact that subjective evaluation of the intensity of a sound is inevitably influenced by the presence and intensity of other sounds. Thus a first sound which is preceded or followed by loud murmurs will be somewhat "masked" and will be assessed as softer than it would in the absence of such a murmur.[4, 6] Secondly, it has been observed that subjective evaluation of intensity is influenced to some extent by the duration of a sound,[6] a factor which does not influence the assessment of intensity ratio recorded by this method.

The results of this study serve to illustrate the reported observation that a loud first sound is an almost invariable feature of mitral stenosis sufficient to produce disturbance of function, and that its absence in mitral disease implies either considerable regurgitation or extensive calcification of the mitral valve.[9] In the present series there was only one exception to this rule.

The results also demonstrate the less well known fact that a loud first sound may be the only abnormality in very mild or early cases. This finding occurring alone should cause the presence of mitral stenosis to be suspected in the absence of the other well known causes of a loud first sound (e.g. thyrotoxicosis, hypertension, pregnancy and rapid atrioventricular conduction).

The second sound in the pulmonary area shows great variability in normal subjects. However, it is evident that it has some diagnostic value when normal variation associated with age is taken into consideration. Although this is accomplished subjectively by the experienced auscultator, it may be difficult, and some workers have found auscultation of the second sound practically valueless in the detection of pulmonary hypertension.[10] Objective measurement provides a cross check on subjective

impression and statistical backing for the probable significance of the results observed.

Summary

A simple method of objective measurement of heart sound intensity has been described and applied to a sufficient number of cases to demonstrate its practicability and potential value.

It has been demonstrated again that a loud first sound is an almost invariable accompaniment of well developed mitral stenosis, that its absence in mitral disease implies the presence of significant regurgitation or extensive calcification of the mitral valve and that it may be the only abnormal feature of early and mild cases.

The value of measurement of intensity of the second pulmonic sound as an index of pulmonary hypertension is limited by the wide range of normality. It was demonstrated, however, that with proper correction for age differences, it is of some value.

Summario in Interlingua

Es describite un simple methodo pro le mesuration del intensitate del sonos cardiac. Le methodo esseva applicate a un sufficiente numero de casos pro demonstrar su practicabilitate e su valor potential.

Esseva demonstrate de novo que un forte prime sono es le quasi invariabile accompaniamento de ben-disveloppate stenosis mitral, que su absentia in morbo mitral indica le presentia de significative regurgitation o de extense calcification in le valvula mitral, e que illo pote esser le sol characteristica anormal de casos inceptive o leve.

Le valor de mesurationes del intensitate del secunde sono pulmonic como indice del hypertension pulmonari es limitate per le extense spectro de normalitate. Nonobstante, nos ha potite demonstrar que caute correcturas pro differentias de etate augmenta su utilitate.

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The Normal P-R Interval in Infants and Children

By MARIANO M. ALIMURUNG, M.D., AND BENEDICT F. MASSELL, M.D.

The value of the P-R interval in the study and evaluation of treatment of rheumatic carditis, a disease predominantly of the younger ages, has prompted a re-examination of the normal P-R standards for infants and children. This study reports these data as obtained from 506 normal infants and children. The data reveal that both age and heart rate exert a significant influence on the P-R interval. The minimum, average, and maximum values are given as related to different ages and different heart rates.

IN previous papers[1-4] we have reported various data on the normal electrocardiogram in infants and children. The same electrocardiographic material offered a valuable source for other analyses, such as the P-R interval.

The P-R interval has been the subject of much interest for many reasons. While not specific for rheumatic carditis, changes in the P-R interval are of significant clinical value in the study of this disease. Thus a prolonged P-R has been described as the most common electrocardiographic finding[5-7] in active rheumatic carditis and occasionally the only evidence of this condition.[8] A marked prolongation is considered by some observers as an indication of a poor prognosis.[9] Shortening of the P-R interval to within normal limits is also valuable in determining subsidence of the rheumatic activity[10] and, therefore, in assessing the success of therapy.[11] In a recent review of 66 patients given corticotropin (ACTH) or cortisone, a prolonged P-R was found to reverse to normal during therapy in 54 instances although in some the P-R prolongation reappeared after the discontinuation of treatment.[12]

A short P-R interval is a characteristic feature of nodal rhythm and of the Wolff Parkinson-White syndrome. In thyrotoxicosis the P-R may also be shortened.

Physiological factors likewise play an important role in determining the P-R interval. Prolongation may be caused by vagotonia; whereas shortening is associated with sympathicotonia.

It is obvious that the normal values of the P-R interval are important in order that the aforementioned clinical applications of P-R changes can be correctly made. Particular emphasis must be placed on the values for children because of the current interest in certain forms of treatment of rheumatic carditis, a disease predominantly of the younger ages.

While there are published data on the normal P-R in children,[13-27] the need for a re-analysis of the subject seems indicated. In many reports attention is mainly directed to the average values of the P-R interval. In others, although the upper limits are specified, the lower limits of normal are not given. In some reports the age grouping followed seems so wide that the existing peculiarities due to age are not clearly appreciated. On the other hand there are reports in which the use of too many age groups makes it difficult to apply the data clinically. Again, there are studies which are limited to infancy alone or which, though concerned with all ages in childhood, are based on a relatively small number of observations; such studies fail to present an adequate picture of the P-R interval for the entire span of infancy and childhood.

In view of the foregoing considerations, the present study was undertaken.

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Clinical Material and Method of Study

In this study, a total of 506 electrocardiograms of normal infants and children ranging in age from birth to 13 years were analyzed. The source of the clinical material and the method used for obtaining the electrocardiographic tracings have been described in our previous publications on other aspects of the normal electrocardiogram in children.[1-4]

For greater accuracy a special reflectoscope was often used in making the measurements. This reflectoscope magnified the tracing to approximately ten times its actual size. In this manner the difficulty of detecting a tiny Q wave was greatly minimized. Particular attention was paid to this point because nonrecognition of a tiny Q wave will lengthen erroneously the P-R measurement. While often called the P-R interval, it is really the P-Q interval that is measured whenever a Q wave is present.

The data herein presented were taken from lead II since nearly all available P-R data in the medical literature are based on lead II measurements. In cases with sinus arrhythmia the average figures for both the P-R interval and the heart rate were the ones considered.

Results

In the first part of this study the average P-R interval was analyzed first in relation to heart rate and then in relation to age.

Figure 1 shows the influence of heart rate on the average P-R for the entire group of 506 infants and children. There appears to be an almost linear trend as the P-R interval shortens with increasing heart rate. At the two extremes are an average P-R of 0.146 second for an average heart rate of 65 per minute and an average P-R of 0.103 second for an average heart rate of 185 per minute.

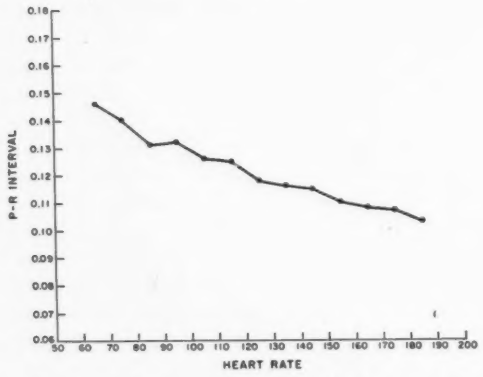

Fig. 1. Influence of heart rate is shown on the average P-R for the entire series without specifically considering the effect of age.

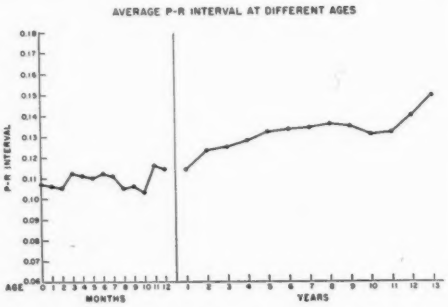

Fig. 2. The average P-R is shown here in relation to age alone, with the first year of life analyzed by months.

Figure 2 presents the relation between the average P-R and age, irrespective of the heart rate in each age. As with the heart rate, there seems to be definite evidence that age also exerts a significant influence on the P-R interval. In spite of certain fluctuations in the curve corresponding to the first twelve months of life, the figures for this age period are still significantly shorter than those in succeeding years. Moreover, as the child grows older, it is evident that the average P-R interval likewise lengthens progressively from an average value of 0.114 second at 1 year of age to 0.15 second at 13 years.

It is generally supposed that a relationship exists between the P-R interval on the one

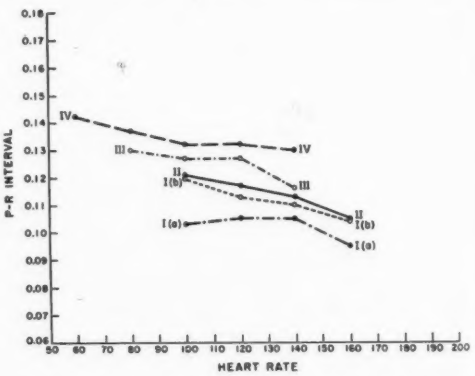

Fig. 3. Average P-R values are shown at different heart rates for the various age groups (see text).

TABLE 1—*Heart Rate*

Age Groups		Below 71				71–90				91–110			
		Cases	Av.	SD	Range	Cases	Av.	SD	Range	Cases	Av.	SD	Range
I	(a) Below 1 month (newborn)									6	.103	.005	.10–.11
	(b) 1–9 months					1	.130			2	.120		.11–.14
II	10 months–2 years									26	.121	.014	.10–.15
III	3–5 years					34	.129	.012	.11–.16	60	.128	.012	.09–.16
IV	6–13 years	24	.142	.014	.11–.18	88	.136	.014	.11–.18	71	.131	.013	.10–.16

		111–130				131–150				Above 150			
		Cases	Av.	SD	Range	Cases	Av.	SD	Range	Cases	Av.	SD	Range
I	(a) Below 1 month (newborn)	7	.106	.005	.10–.11	7	.106	.005	.10–.11	6	.098	.007	.09–.11
	(b) 1–9 months	14	.114	.007	.10–.13	33	.107	.008	.09–.12	13	.104	.005	.10–.11
II	10 months–2 years	40	.117	.012	.10–.14	25	.114	.011	.10–.14	7	.100	0	.10–.10
III	3–5 years	21	.128	.014	.10–.16	7	.116	.010	.10–.13				
IV	6–13 years	13	.134	.013	.12–.16	1	.130						

Average values as well as the range (minimum and maximum limits) of the P-R interval are given for the different age groups and for different heart rates. The number of observations is also given for each age group with heart rates within the heart rate range indicated.

hand and heart rate and age on the other. Such a relationship is substantiated by the curves just presented. In the second part of this study, therefore, an analysis was made of the combined effects of age and heart rate on the P-R interval. In order to accomplish this purpose, it was necessary to divide the cases into certain age groups. Since any age subdivisions would necessarily have to be arbitrary, it was decided to follow the same age groupings that we had used in previous reports[2, 3] on other data of the normal child's electrocardiogram. These age groups are as follows: Group I, from birth to 9 months; group II, from 10 months to 2 years; group III, from 3 to 5 years and group IV, from 6 to 13 years. The newborn (under 1 month of age) were further separated into another subgroup within group I because of the comparatively shorter P-R intervals noted in the first month of life.

Figure 3 shows the relation of the average P-R interval to heart rate for each age group. It is evident that the P-R interval is longer in the older ages for any given heart rate. Thus, for instance, at a heart rate of 120 per minute the average P-R interval is 0.106 second for the newborn, 0.114 second for children between 1 month and 9 months, 0.117 second for those between 10 months and 2 years, 0.128 second for ages 3 to 5 years, and 0.134 second for 6 to 13 years of age.

Finally in table 1, the same data depicted in figure 3 are shown together with the range of the P-R interval and the standard deviation for those groups in which a sufficient number of cases allowed for its calculation. In this table it is shown that, on the whole, at any given heart rate the maximum as well as the average values for P-R were longer for the older ages. Not shown in table 1 is that only one child had a P-R of 0.18 second at rates below 71 and only one child each had P-R intervals of 0.18 and 0.17 second in the heart rate range between 71 and 90 per minute. In contrast to the average and maximum values the minimum limits do not vary appreciably with age and with heart rate. It should be noted that the number of observations, as shown in the table, was small for some of the groups of cases.

DISCUSSION

The influence of age on the P-R interval is well accepted. The fact that the heart of a child is many times smaller than that of an

adult explains why the P-R is significantly shorter in a child than in an adult. Studies on adults further indicate that the P-R increases with age even at constant heart rates, especially "in the second and the fifth to sixth decades." This observation[28] was recently substantiated by Packard, Graettinger and Graybiel[29] in their follow-up study in 1950 on healthy aviators, whom they had previously examined in 1940. These authors noticed an increase of the mean P-R from 0.154 to 0.159 second in spite of an increase of average heart rate from 64 to 75 per minute. At any given heart rate the 1950 mean P-R was consistently longer than the 1940 value. Careful study of their data led these authors to the conclusion that the difference noted was not due to chance or to change in either blood pressure or body weight but was most likely due to "some factor associated with aging."

That the P-R interval is likewise influenced by heart rate is also generally supposed. In fact some workers have proposed formulae to express the relationship between heart rate and P-R.[30] Obviously such formulas cannot express completely the standards for the P-R interval unless the role of age is simultaneously represented. Other authors[31, 32] doubt that there is an important influence of heart rate on the P-R interval.

As far as our own findings are concerned, there seems to be sufficient indication that, at least in infants and children, both age and heart rate exert a definite influence on the P-R interval. What factor has a greater influence cannot be determined from our study. Nevertheless, it is evident from our data that observations relating the P-R interval to either age or heart rate alone are unsatisfactory especially if such data are to be applied clinically.

The lower limit of the normal P-R interval has not been studied as much as the upper limit. Thus Kossman[33] has recently stated that "a precise definition of the lower limit must await more precise statistical study." In our study, therefore, the data for the lower limit of the P-R interval were also collected.

An attempt was made to compare our results with those of other reports in the medical literature. This comparison could be done only to a very limited degree because of two main reasons. First, in some reports the P-R interval was studied in relation to either heart rate or age alone but not to both. Second, when consideration was given to both age and heart rate, the age grouping followed was different from that used in our study.

Such a limited comparison could be made with the data furnished by Ashman and Hull.[34] Their table, a widely used reference for the normal values of the P-R interval, provides data on the upper limits of the normal P-R for various age groups, including children and adults, and for various heart rates. As far as the comparison was feasible, it can be noted that our data are very similar to those of Ashman and Hull. Thus, for instance, for children between 7 and 13 years of age, Ashman and Hull give for upper limits of P-R 0.18 second for rates below 70 per minute, 0.17 second for rates between 71 and 90, 0.16 second for rates between 91 and 110, and 0.15 second for rates between 111 and 130. Our data for the comparable age group, 6 to 13 years, show upper limits for P-R of 0.18 second, 0.18 second, 0.16 second, and 0.16 second for corresponding heart rates. The other age groupings for younger children, new born to 1½ years and 1½ to 6 years, followed by Ashman and Hull are different from our age grouping in this age span; hence, no comparison could be made in these age periods. Furthermore, our data suggest that more age subdivisions are needed in the younger ages. Finally, Ashman and Hull do not furnish the average and minimum values of the P-R in their table.

Summary

Because of the value of the P-R interval in evaluating the treatment of rheumatic carditis, a disease occurring predominantly in the younger age groups, the normal P-R for infants and children was re-examined. This study was based on the electrocardiograms of 506 normal infants and children, ranging from birth to 13 years of age.

Both age and heart rate were found to exert a significant influence on the P-R interval.

Normal values must therefore be related to both factors.

The average normal P-R interval and the minimum and maximum limits of normal for various age groups and for different heart rates are given.

Acknowledgment

The authors are indebted to Dr. Lester G. Joseph of New Haven, Conn., who took the electrocardiograms used in this study at the Children's Medical Center, Boston, (1947 and 1948); to Dr. Jane Worcester, Assistant Professor of Biostatistics, Harvard School of Public Health, for her valuable advice on the statistical aspects of this study; to Miss Rita Nickerson for the statistical calculations; and to Dr. Fred M. Snell for devising the special reflectoscope used in this study.

Summario in Interlingua

A causa del signification del intervallo P-R in evalutar le tractamento de carditis rheumatic—un morbo que occurre predominantemente al etates plus juvene—le norma de P-R pro infantes e juveniles esseva re-examinate. Nostre studio es basate super le electrocardiogrammas de 506 infantes e juveniles normal, de etates ab infra un mense usque a 13 annos.

Il esseva constatate que le etate e le frequentia cardiac exerce un influentia significative super le intervallo P-R. Valores normal debe consequentemente esser relationate a ambe iste factores.

Nos lista le valor median del normal intervallo P-R e le limites minimal e maximal del norma pro varie etates e varie frequentias cardiac.

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A Comparative Study of Spatial Vectorcardiograms Obtained with the Equilateral Tetrahedron and a "Corrected" System of Electrode Placement

By J. A. Abildskov, M.D., and Eldon D. Pence, M.D.

Spatial vectorcardiograms of a group of normal young adults, recorded with two systems of electrode placement, have been studied. Those recorded with the equilateral tetrahedron as the reference system were similar to records previously described and had QRS-loops of two configurations. Those recorded with a method of lead placement designed to reduce the errors inherent in the commonly used reference frames had greater uniformity of form and orientation of both the QRS and T-loops.

IT IS well known that many assumptions inherent in representing the human body as a regular geometric figure are only approximations. The concept of so representing the body has been extremely useful in electrocardiography despite errors introduced by these simplifying assumptions, but it is nevertheless desirable to eliminate or minimize these errors. This is especially important in studies of the spatial vectorcardiogram which it is hoped will extend the range of usefulness of electrocardiography.

By application of the reciprocity theorem of Helmholtz to experimental data obtained with fluid mappers representing the body, McFee and Johnston have designed a system of electrode placement which appears promising as a method of reducing some of the errors in electrocardiography.[1-3] Briefly stated, this "corrected" lead system depends on effectively modifying the form of the lead fields in the body by the use of multiple electrodes at such sites that the fields will be altered in the desired direction. For example, the lead field of standard lead I is effectively modified by connecting the electrode on the right arm to an electrode on the right side of the chest, and that on the left arm to an electrode on the left side of the chest, with each electrode in series with a large resistance. The studies of McFee and Johnston indicate that the lead field of the two electrodes on the sides of the chest has characteristics which tend to cancel the undesirable features of the lead field of standard lead I.

A combination of electrodes at sites chosen to modify the anteroposterior lead field in the sagittal plane in the desired direction has also been suggested by these workers. This consists of multiple chest electrodes placed in front of, and behind, the heart, and the horizontal component in the sagittal plane obtained with this lead system represents the potential difference between the anterior and posterior electrodes.

The present study has no direct bearing on the validity of either of the lead systems employed. The purpose of the study was to obtain clinical experience with the recently suggested lead system, and to compare vectorcardiograms and electrocardiograms obtained with this system and those obtained with the equilateral tetrahedral method of electrode placement. This appeared desirable, both as a foundation for possible future clinical application of the new system and as an aid in defining the potential usefulness of the system.

Materials and Methods

Studies were made on 75 male subjects in the age range of 18 to 35 years. A medical history, physical

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examination, teleroentgenogram of the chest and electrocardiogram, including standard and unipolar limb leads and precordial leads V_1 through V_6, were obtained on each subject. None of the subjects had evidence of cardiovascular disease.

Spatial vectorcardiograms were obtained on each subject using both the equilateral tetrahedral system of electrode placement and the "corrected" leads devised by McFee and Johnston to obtain the horizontal (x and z) components in the frontal and sagittal planes. Leads V_F was utilized as the vertical (y) component of the vectorcardiogram with both electrode systems.

With the equilateral tetrahedron as a reference frame, frontal and left sagittal plane projections of the vectorcardiogram were recorded simultaneously from two cathode ray oscilloscopes. Superior plane and frontal stereoscopic views obtained by the method of Cronvich and coworkers were also recorded.[4] Standardizing factors appropriate to this reference frame were employed. These were such that 1 mv. introduced in the vertical deflecting circuits produced a deflection of 1.7 units and when introduced in the horizontal deflecting circuits produced a deflection of 1 unit on the oscilloscope used to record the frontal and 1.2 units on the oscilloscope used to record the left sagittal plane projection. For the stereoscopic views the standardizing factors were such that 1 mv. introduced in the horizontal deflecting circuits produced a deflection of 1 unit and introduced in the vertical deflecting circuits a deflection of 1.7 units on both oscilloscopes. With this electrode system, connections were such that relative positivity of the left arm in the frontal plane and of the back electrode in the sagittal plane produced a deflection of the beam to the left (the observer's right) and relative positivity on the left leg produced a downward deflection in both frontal and sagittal planes.

Frontal and left sagittal plane projections were recorded simultaneously, using the "corrected" lead system. As employed in this study, the horizontal component (x) of the frontal plane projection was furnished by a lead composed of electrodes on the left arm and a point on the left midaxillary line at the level of the ensiform cartilage, each in series with a large resistor and connected together, and a similar pair of electrodes on the right arm and the right side of the chest. The sagittal component (z) of the vectorcardiogram was represented by the potential difference between two banks of nine electrodes each, placed opposite each other on the anterior and posterior surfaces of the chest. The electrode banks were so placed that the center of the posterior bank was located 2 cm. to the left of the seventh dorsal vertebra. Each electrode bank measured 12 by 12 cm. and each electrode was German silver and measured 1 by 1 cm. Each electrode was in series with a large resistance and all electrodes comprising each bank were connected together beyond the resistors. The vertical component of both frontal and sagittal projections was furnished by lead V_F.

Standardizing factors employed with the "corrected" method of electrode placement were such that 1 mv. introduced in the horizontal deflecting circuits produced a deflection of 1 unit on both oscilloscopes and 1 mv. introduced in the vertical deflecting circuits produced a deflection of 1.7 units. With this electrode combination, relative positivity of the electrode pair on the left arm and left side of the chest and of the electrode bank on the posterior surface of the chest produced a deflection of the electron beams to the left (the observer's right), and relative positivity of the left leg produced a downward deflection.

The large resistances in series with the multiple electrodes employed in the "corrected" lead system act to average the potential at the electrode sites without distorting the electric field by production of large isopotential areas. To adequately accomplish this, it is necessary that these resistances be approximately equal. Since the skin resistance at each electrode site acts in series with a resistor in the external network it is desirable that the value of the skin resistance be low relative to the network resistors. Inequalities in the values of skin resistance are minimized if the external network resistances are high. Thirty-five of the records included in this study were obtained with a 50,000 ohm resistor in series with each electrode site making up the "corrected" leads. For the remaining 40 records, each resistor had a value of 1 megohm which further reduced the effect of unequal skin resistances at the electrode sites.

The amplifiers employed in this study were standardized by application of the calibration voltage to the cathodes of the input tubes. Using this method of calibration with the resistor networks employed in the "corrected" leads, it is necessary to consider the effect of the networks on the magnitude of records if they are to be compared to those obtained with other reference frames. The effect of the resistor networks on the magnitude of the records can be expressed as:

$$\frac{eo}{ei} = \frac{Ri}{\sum Rex + Ri}$$

where: eo = effective voltage delivered to amplifier
ei = effective voltage at the electrodes
Ri = input impedance of amplifiers
Rex = effective external resistances in the network

The amplifiers employed in this study had an input impedance of 4.7 megohms in the relevant frequency range. With the standardizing factors employed, the horizontal component of the frontal plane projection of the 35 records obtained with 50,000 ohm resistors in the networks was 0.5 per cent less than the proper value. The horizontal

component in the sagittal plane of these records was 0.2 per cent less than the proper value. In the 40 records obtained with 1 megohm resistors in the networks, the horizontal component in the sagittal plane was 2 per cent less than the correct value. For the purposes of this study, these errors were considered insignificant and no corrections were made. The horizontal component of the frontal plane projections in the records obtained with 1 megohm resistors in the networks was 10 per cent less than the proper value, and measurements of maximal QRS and T vectors from these records were corrected geometrically.

In all records, time was indicated by interrupting the oscilloscopic trace 400 times per second, and shaped segments of the trace with the blunt end of each segment in the lead indicated the inscription direction.

Each of the plane projections and the stereoscopic views of the vectorcardiogram were inspected and the general contour, magnitude and orientation of the QRS- and T-loops were noted. The direction of inscription of the QRS-loops in frontal and sagittal plane projections was also noted. Three-dimensional wire models representing each QRS-loop recorded with both electrode systems were constructed to conform to the plane projections. The magnitude and orientation in a triaxial reference system of the longest vector of the QRS- and T-loops were measured in the frontal and left sagittal plane projections. In the case of the left sagittal plane projection the ±180 degree axis of the triaxial reference system was considered to be located anteriorly. Finally the maximal extension of the QRS-loop behind a vertical line through the isoelectric point was measured in millivolts.

All observations and measurements made on vectorcardiograms obtained with the equilateral tetrahedron reference frame were compared with those on records made with the "corrected" lead system. Electrocardiograms showing simultaneous horizontal (x and z) and vertical (y) components of the frontal and sagittal plane projections of the vectorcardiograms recorded with the two lead systems were also compared.

Results

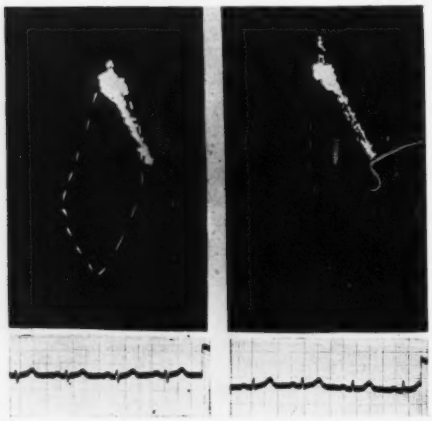
QRS-Loop

(1) *Contour*. It has been previously reported that the QRS-loops of normal subjects in the age group represented in this series, recorded with the equilateral tetrahedral reference frame, could be divided into two groups on the basis of spatial configuration.[5] These loops were designated as "type 1" when they were elliptoid figures whose maximum width was approximately one-third of the greatest length, and "type 2" when the loops were characterized by a greater enclosed area behind the isoelectric point and had a roughly circular spatial outline. In the reported series, 88 per cent of the QRS-loops were of the "type 1" and 12 per cent of the "type 2" configuration.

Similar results were obtained in the present series of QRS-loops recorded with the tetrahedral electrode placement. Sixty-three (84 per cent) of the QRS-loops had elliptoid spatial configurations and were classified as "type 1". Twelve (16 per cent) of the loops had the configuration previously designated as "type 2" with roughly circular spatial outlines and large enclosed areas behind the isoelectric point.

The QRS-loops of vectorcardiograms obtained with the "corrected" lead system showed no such division into "types". Variations in spatial orientation and minor variations in contour resulted in differences in the form of planar projections of the loops, but the major features of spatial configuration were similar.

The vectorcardiograms of 58 subjects whose routine electrocardiograms showed a normal electrical axis or left axis deviation had only minor differences in the contour of frontal plane projections of the QRS-loops recorded with the tetrahedral and "corrected" lead systems. Definite differences in the configuration of the frontal plane projection of the QRS-loops of the remaining 17 subjects were present. The routine electrocardiograms of all of these subjects showed a moderate or marked right axis deviation with deep S waves in lead I, and the frontal plane projections of the QRS-loops enclosed large areas to the right of the isoelectric point. In contrast the same projection of the QRS-loops recorded with the "corrected" lead system enclosed smaller areas to the right of the isoelectric point, and the "corrected" lead I of these subjects had only shallow S waves. These findings are illustrated in figure 1. The frontal plane projection of a vectorcardiogram recorded with the equilateral tetrahedron and its horizontal scalar component (lead 1) are shown in figure 1*A*. It may be noted that this



A *B*

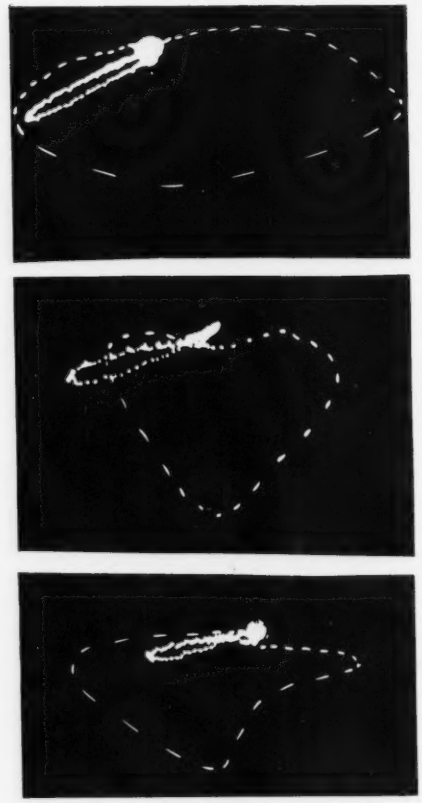
FIG. 1. *A* shows the frontal plane projection of a vectorcardiogram with the equilateral tetrahedron from a subject whose electrocardiogram showed right axis deviation. Standard lead I of the electrocardiogram is also shown. In *B* the frontal plane projection of the same subject's vectorcardiogram recorded with the "corrected" lead system is shown together with its horizontal scalar component.

projection of the QRS-loop enclosed a large area to the right of the isoelectric point and that lead I has a deep S wave. Figure 1*B* shows the frontal plane projection and the horizontal scalar component of the vectorcardiogram of the same subject recorded with the "corrected" electrode placement. In this vectorcardiogram the area to the right of the isoelectric point is smaller and only a small S wave is present in "corrected" lead I.

The sagittal plane projections obtained with the "corrected" leads were remarkably similar to each other, and differed considerably from those recorded with the tetrahedron.

The "type 1" QRS-loops recorded with the tetrahedron had elliptoid configurations in the sagittal plane while those classified as "type 2" had more complex contours in this plane with a large enclosed area behind the isoelectric point. The general form of the sagittal plane projection of QRS-loops recorded with the "corrected lead" systems was roughly triangular. The initial and terminal portions of the loop formed one side and the mid portions of the other two sides of this figure. The major variations of contour of the "corrected" QRS-loop in the sagittal plane are illustrated in figure 2.

The similarity of QRS-loops recorded with the "corrected" lead system was most apparent in the three dimensional models constructed to conform to the plane projections of the vectorcardiogram. The finding is best illustrated by comparing the contour of the "corrected" QRS-loops of two subjects whose QRS-loops obtained with the tetrahedral reference frame were of the "type 1" and "type 2" varieties. Figure 3 shows an example of such records. In figure 3A the frontal and sagittal plane projections of a "type 1" QRS-loop obtained with the tetrahedral reference frame are shown



A

B

C

FIG. 2. The major variations in contour of the left sagittal plane projections of vectorcardiograms recorded with the "corrected" system of lead placement are illustrated. *A* shows a form in which the maximal vector is directed posteriorly, while in *B* this vector is directed downward and in *C* is directed forward.

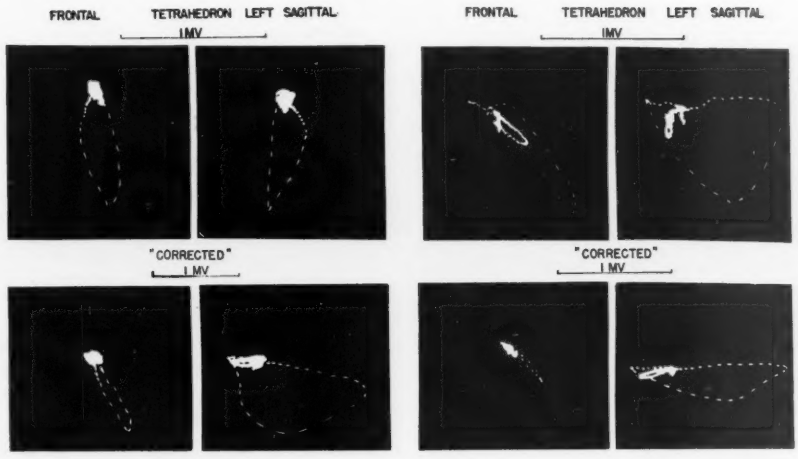


FIG. 3. *A* shows the frontal and left sagittal plane projections of a vectorcardiogram with a "type 1" QRS-loop recorded with the equilateral tetrahedron, and these views of the vectorcardiogram of the same subject obtained with the "corrected" lead system. *B* shows the same views of a vectorcardiogram with a "type 2" QRS-loop recorded with the equilateral tetrahedron and those of the same subject obtained with the "corrected" leads.

above these views of the same subject's vectorcardiogram recorded with the "corrected" leads. Figure 3*B* shows similar views of a "type 2" QRS-loop recorded with the tetrahedron and those recorded on the same subject with the "corrected" leads. The greater similarity of vectorcardiograms obtained with the "corrected" leads is apparent.

(2) *Orientation.* Variations in orientation about the anteroposterior, transverse and longitudinal axes of the loops were found in records obtained with both reference frames. With present methods it is difficult to quantitate variations in orientation of spatial vectorcardiograms. The direction of the maximal QRS vectors in frontal and sagittal planes is not adequate to indicate the orientation of records having variable form. Wide variations in the orientation of the maximal vectors of records obtained with both reference systems were found but the general impression from simple observation of the planar projections and the spatial models was that less variation in overall orientation was encountered in the records obtained with the "corrected" lead system.

(3) *Magnitude.* The major difference in the magnitude of QRS-loops obtained with the tetrahedral and the "corrected" lead systems was in the area enclosed by the sagittal plane projection. Considerably greater areas were enclosed in the "corrected" sagittal projections and this difference was reflected in measurements of the magnitude of maximal QRS vectors. The average maximal vector in the sagittal plane projection of records obtained with the tetrahedron was 0.78 mv. while that in records obtained with the "corrected" lead system was 1.12 mv. This difference in the magnitude of the sagittal plane projection of the QRS-loops obtained with the two electrode systems was also reflected in the measurements of the "maximal posterior extent" by which is meant a measurement from the most extreme posterior portion of the loop to a vertical line through the isoelectric point of loops. The "maximal posterior extent" of QRS-loops recorded with the tetrahedron ranged from 0 to 1.15 mv. with an average value of 0.32 mv. while that of records obtained with the "corrected" leads ranged from 0.22 mv. to 2.4 mv. and averaged 0.92 mv.

T-Loops

One of the marked differences in the records obtained with the two reference frames was in the contour, orientation and magnitude of T-loops in the sagittal plane projection. In records obtained with the tetrahedron the T-loops were elliptoid or roughly circular outlines and were directed downward and either slightly forward or backward. T-loops in the sagittal projection of records obtained with the "corrected" lead system were uniformly elliptoid in outline, were directed anteriorly and were larger than T-loops obtained with the tetrahedron. The average magnitude of the maximal vector of T-loops recorded with the tetrahedron was 0.29 mv. in the frontal and 0.19 mv. in the sagittal plane, while that of T-loops obtained with the "corrected" electrode placement was 0.34 mv. in the frontal and 0.53 mv. in the sagittal plane. Examples of the contour of T-loops obtained with the two electrode systems may be seen in figures 1 to 3. In both contour and orientation, T-loops recorded with the "corrected" lead system differed less from one another than did T-loops recorded with the equilateral tetrahedron.

Discussion

The results of this study do not constitute direct evidence for the superiority of either of the electrode systems employed. It is very likely that significant errors in sampling the components of the electric field produced by the heart occur with both systems. However the studies of McFee and Johnston indicate that the electrode combinations they have suggested operate to reduce these errors. The concept of utilizing multiple lead fields whose undesirable features tend to cancel appears to be a potentially important one and clinical observations with electrode combinations based on this concept seem to be indicated.

In this study electrocardiograms and vectorcardiograms obtained with the new electrode combinations have been compared with those recorded with the equilateral tetrahedral reference frame. Differences in configuration, orientation and magnitude were all encountered.

The configurations of vectorcardiograms recorded with the equilateral tetrahedral reference frame were of two general types, as has been previously reported, while the major features of spatial configuration of vectorcardiograms obtained with the "corrected" lead systems were similar. This finding is of particular interest since Gardberg's studies concerning the effect of eccentricity of the heart on the electrocardiogram and vectorcardiogram led him to suggest that the division of vectorcardiograms recorded with the tetrahedral method of electrode placement into two groups is an artefact related to the proximity of an electrode on the back to the heart.[6]

The vectorcardiograms and electrocardiograms obtained with the "corrected" lead system on subjects whose routine electrocardiograms showed right axis deviation are also of special interest. Both the form and orientation of these QRS-loops differed less from the remainder of records obtained with this lead system than did those obtained with the tetrahedron from other QRS-loops recorded with the same reference system. The conventional standard lead I of these subjects showed large S waves, while in the "corrected" lead I of the same subjects the S waves were small as is more common in lead I of normal subjects. Although it could not be quantitated in this study there appeared to be less variation in spatial orientation of QRS-loops recorded with the "corrected" lead system than in those obtained with the equilateral tetrahedron. There was definitely less variation in orientation and contour of T-loops obtained with the "corrected" lead system than in those recorded with the tetrahedral electrode placement.

The finding of greater uniformity among vectorcardiograms obtained with the lead system suggested by McFee and Johnston than in the records obtained with the tetrahedron, while not direct evidence, is consistent with the view that less distortion of the electric field of the heart is associated with use of these "corrected" leads. Studies designed to quantitate the errors involved in the use of multiple lead fields to obtain components of the "heart vector" and to define the optimal

lectrode combinations, as well as further linical studies of both normal and abnormal ubjects, will be necessary to assess the im-ortance and usefulness of the concept in-olved.

Summary

Spatial vectorcardiograms of 75 normal oung males, obtained with the equilateral etrahedral reference frame and with a "cor-ected" lead system suggested by McFee and ohnston, have been compared. The study vas undertaken to provide clinical experience vith the latter lead system and has no direct earing on the validity of that system.

As previously reported, QRS-loops recorded with the tetrahedral reference frame could be divided into two groups on the basis of spatial configuration. Orientation about all axes of the loops varied. T-loops in records recorded with the tetrahedron were elliptoid or roughly circular and the maximal vectors were directed downward, to the left and either slightly forward or backward.

In contrast the QRS-loops recorded with the "corrected" lead system showed considerable similarity to each other and appeared to have less variation in spatial orientation. The area enclosed by the sagittal plane projection of the QRS-loops was much greater in records obtained with this reference system than in those recorded with the tetrahedron. T-loops recorded with this reference system were uniformly long elliptoid outlines directed to the left downward and forward.

Summario in Interlingua

Duo systemas de placiamento del electrodos esseva usate in le registration de vectocardiogrammas spatial ab un gruppo de normal juvene adultos. Le registrationes obtenite con le uso del equilatere tetrahedro como systema de referentia esseva simile a previemente describite registrationes e exhibiva ansas QRS de duo configurationes. Le registrationes obtenite con le uso de un placiamento del derivationes destinate a reducer le errores inherente in le currente systemas de referentia[1] exhibiva un plus uniforme configuration e orientation del ansas QRS e etiam del ansas T.

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Report of Committee on Blood Vessel Banks

Recommendations for the Establishment and Maintenance of a Blood Vessel Bank

VASCULAR GRAFTS

Introduction

Space Requirements

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(2) *Without Sterile Precautions.*

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RIGID AND FLEXIBLE PLASTIC PROSTHESES

Introduction

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SUMMARY

MODERN advances in the diagnosis and surgical correction of cardiovascular lesions have made the procurement, preservation and implantation of blood vessel grafts an important factor in the success of such surgery.

It soon became evident that survival of cells in a graft after implantation was not an indispensable element for satisfactory functional results in patients wherein growth of the graft is not necessary. Therefore, recent efforts have been made in the direction of determining which method of preservation of vascular grafts is most satisfactory. It should be realized, however, that further investigations are necessary, and that only long-term postoperative observation in human recipients will give a definitive answer on the fate of the various types of vascular and plastic prostheses that have been advocated.

The following recommendations have been prepared with the idea of aiding clinical investigators in the establishment of blood vessel banks under standard conditions and, as far as possible, to adopt a certain uniformity in the procurement and preservation of vascular grafts for future evaluations.

Space Requirements

Depending on the type of preservation to be used, space requirements can be reduced to a minimum of one room, measuring approximately 24 by 16 feet. To lessen possibilities of bacterial contamination, it is desirable to set up a small compartment of about 8 by 10 feet for the manipulation of sterile grafts under ultraviolet light.

For the use of ethylene oxide as a sterilizing agent, the work should be carried out under a hood or in a fireproof cubicle on an adjacent terrace with an exhaust fan for adequate ventilation. This is an important safety measure, because the fumes are highly explosive.

General Equipment: Sterile or Clean, Depending on the Method of Procurement

Glass Flasks. For the preservation and transportation of the specimens, pyrex glass flasks of about 500 ml. capacity with wide mouth are desirable. The type with rubber sleeve-diaphragm top is adequate.* (See section in freeze-drying process.)

* Fenwal type, obtainable from MacAlaster Bicknell Co., Cambridge, Mass.

Test Tubes. For culture (if sterile technic is employed).

Surgical Equipment. Two Scalpels no. 10 and no. 15 blades, 1 Mayo scissors medium size, 6 hemostatic clamps, 6 mosquito clamps, 1 Metzenbaum scissors, 2 arterial thumb forceps, 2 Harrington retractors, 1 Finocchietto retractor, 2 kidney basins, umbilical tape and bowel clips.

Linen. Four towels and four sheets.

Solutions. Ringer's and isotonic Salt. For preservation, a 12 cubic foot deep-freeze unit with supply of dry ice is necessary.

Procurement of Material

(A) *Legal Aspects*

Depending upon local regulations in different communities, it is generally understood that special permission for the removal of tissues for therapeutic purposes must be signed by the relatives of the deceased. Such a form utilized by the New York Blood Vessel Bank is shown in figure 1 and is supplied with the regular permission for autopsy. The significant increase in the use of these procedures and indoctrination of the public in the importance of cooperation in this regard, will facilitate the fulfillment of legal requirements.

(B) *Surgical Technics*

Although the removal of blood vessels will be quite similar, whether taken with or without sterile precautions, the former involves several additional requirements in order to avoid contamination.

(1) *Under Sterile Precautions.* Surgical perforated drums or packs containing instruments and linen must be prepared and sterilized ahead of time. Personnel requirements include two surgeons and a nurse. Strict sterile surgical technic must be followed. The skin is shaved and prepared with Phisohex,* rinsed with water and then with an aqueous solution of benzalkonium chloride, 0.1 per cent, three times.

Sterile sheets are then applied, covering the entire body except the area of incision. This is usually a combined thoracoabdominal incision with a U-shaped thoracic component and an abdominal incision from the xiphoid to pubis. The left thoracic cavity is entered by dividing the ribs at the costochondral junction. The ribs on the right side are similarly sectioned without entering the right pleural space to lessen the possibilities of contamination. A midline abdominal incision is made from the xiphoid to the pubis, passing to the left of the umbilicus. Care is taken not to incise the peritoneum. The surfaces of the left lung, parietal pleura and mediastinum are carefully inspected. A specimen of the pleural fluid is taken for culture. An assistant retracts the left lung and mediastinum to the right. The left diaphragm is incised as close to its insertions as possible and the peritoneum is also retracted to the right for a retroperitoneal exposure of the abdominal aorta. The aorta and its branches are mobilized, sectioning the branches as far as possible from the aorta to facilitate the application of ligatures later when the graft will be implanted. The abdominal aorta at the bifurcation should be handled with extreme care to avoid any traction on the common iliac arteries. The external iliacs are sectioned at the level of the inguinal ligaments. Further incisions are made for resection of femoral or axillary arteries. The carotid arteries can be resected subcutaneously through the chest incision. In all cases a rubber or glass tube is connected to the distal end of each artery and vein in order to facilitate embalm-

_____
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Date_____19__

THE UNDERSIGNED,_____OF THE DECEASED,
(Relationship)
CONSENTS TO REMOVAL OF SECTIONS OF BLOOD VESSELS OF THE DECEASED,

_____
(Name of Deceased)
FOR SUCH SCIENTIFIC AND THERAPEUTIC PURPOSES AS THE MEDICAL STAFF OF THE _____MAY DEEM DESIRABLE.

_____ _____
(Witness) (Signature)

FIG. 1

* Winthrop Sterns Inc., New York, N. Y.

ing by the undertaker. The arteries are cleaned of excessive connective tissue but the adventitia must be preserved.

The entire aorta is divided into segments, depending on its future application, in general, (1) entire arch of the aorta, (2) descending thoracic aorta to the diaphragm, (3) abdominal aorta including bifurcation and external and internal iliac arteries and (4) femoral and axillary arteries. If vein grafts are desired, the entire inferior vena cava can be taken through the same incision. Cultures are now taken from the various arterial segments.

Unless the part of the aorta which includes the celiac axis is going to be used as a graft, it is isolated and sent to the laboratory in 10 per cent formalin-Ringer's solution for studies of fat, elastic fibers and the usual histopathologic sections. A segment of the ascending arch of the aorta is of value in giving further information on the degree of atheromatosis of the vessels.

Although histologic study of segments of the donor's aorta is not an essential feature in the practical management of a blood vessel bank, it is our belief that information may be obtained which will serve as a guide to delineate possible limitations to the use of arterial grafts.

The grafts are rinsed in Ringer's solution and placed without further treatment into empty sterile pyrex flasks with rubber tops and transported to the Bank.

The taking of vessels under sterile precautions (as outlined in the preceding section) is usually a nuisance to the pathologist and hence is falling more and more into disuse. It has been found that it is completely acceptable, and is widely practiced, to take the vessels without sterile precautions, so that one can get out of the pathologist's way, and then sterilize the grafts subsequently by some suitable method.

(2) *Procurement Without Sterile Precautions.* Only one surgeon and assistant are required for the technical procedure. The same exposure is utilized without cleansing the skin, and draping it is less rigidly practiced. It is important to emphasize, however, that excessive contamination must be avoided, particularly from any gastrointestinal contents and, if possible, the retroperitoneal approach described above should be used. The handling of arteries is the same. However, no bacteriologic cultures are taken at this time.

(C) *Evaluation of Donor Material*

Three factors must be considered in the evaluation of vascular specimens: (1) age of donor, (2) cause of death and (3) the interval between death and autopsy.

(1) *Age of Donor.* Although there is some value in establishing a limit on the age of the donor, it is a common observation that there may be little correlation between the donor's age and the degree of aortic degeneration. A considerable number of persons under 30 years of age have significant pathologic changes in the aortic wall in contrast with some of 50 years or more with surprisingly slight degeneration, especially women. It seems, however, that 45 years is an advisable upper age limit for the great majority of donors. It is important to emphasize at this point, that only a careful pathologic study in each particular case will give a definitive answer to this question.

(2) *Cause of Death.* If an atherosclerotic process such as myocardial infarction has been responsible for the individual's death, then his arteries will not, as a rule, be good donor material. An infectious disease in the donor which might possibly be transmitted by a graft to the host should be excluded. Examples are infectious and homologous serum hepatitis, syphilis, generalized sepsis and malaria. Patients dying of one of the collagen diseases should be rejected as donors. When death is due to a neoplastic disease other than a brain tumor, the body is not suitable.

The ideal donor is an individual whose death resulted suddenly from trauma. A second favorable source of material is the drug addict whose death followed an overdose of narcotic. The true limitations of donor material will be delineated, however, only by the utilization of grafts from donors, presently considered unsuitable, and by careful follow-up of the recipients.

(3) *Interval between Death and Autopsy.* It has been shown conclusively by tissue culture

studies that the viability of cells of the arterial wall is highly reduced if the vessels are removed six hours or more after death, and that the incidence of contamination from the intestinal tract is increased. Although, as previously mentioned, bacterial contamination is not considered of fundamental importance any longer, it is evident that damage to the arteries may occur in a few hours if the body is kept at room temperature, particularly during hot weather. Successful transplantation of blood vessels, taken up to 36 hours after death, have been reported and, as in the case of the donor's age, histologic studies may assist in the evaluation of each particular graft. Nevertheless, it is advisable to remove the vessels within six hours after the death of the subject.

Sterilizing Agents

In order to sterilize vascular grafts taken without sterile precautions different methods can be used. It is evident that we as yet do not have the ideal agent which is effective against all forms of microorganisms, spores and viruses and at the same time produces minimal histologic and functional changes in the vascular wall. Sterilizing agents can be divided into chemical and physical.

Chemical Agents

Two agents which have been tested extensively both clinically and experimentally will be described.

Ethylene Oxide. Chemical Data. This is the simplest epoxy compound, $H_2CO—CH_2$, boils at 10.8 C. and freezes at −111.3 C., is a gas at ordinary temperatures but is quite easily liquefied; is colorless and has a rather pleasant ethereal odor. It is soluble in all proportions in water and in usual organic solvents and can be obtained* as a liquid in low-pressure steel cylinders or in 100 ml. sealed glass bottles. Storage in electric refrigerators should not be attempted, because of the danger of an explosive mixture with air in all proportions from 3 to 80 per cent.

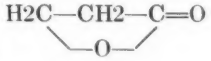
Toxicity: Ethylene oxide produces marked irritation of the respiratory system, and careful avoidance of contact with the skin during manipulation, as described in space requirements, in a well ventilated fire-proof cubicle with exhaust fan capable of changing the total air of the room every two to three minutes or under a hood is important. Clinical cases of accidental poisoning in man after industrial use have been described.

Way of action: As postulated by Phillips, action should occur by alkylating free-carboxyl, amino, sulfhydryl and hydroxyl groups of the protein keratin, replacing the labile hydrogen on each of these groups with an hydroxyethyl radical.

Method of sterilization with ethylene oxide: After the vascular segments, taken without sterile precautions and frozen, are in the bank, they are placed in individual sterile pyrex flasks of 500 ml. capacity, or in the special pyrex tubes for the freeze-drying process. Sufficient liquid ethylene oxide to fill the entire container is added and maintained for 30 minutes. This must be done under a hood or fireproof cubicle as indicated previously. If room temperature is above 30 C., the flasks are placed in an ice bath (2 to 4 C.). The vessels must be completely immersed in ethylene oxide during the entire period of sterilization and more should be added if evaporation is too rapid.

The residual ethylene oxide is decanted and the vessels rinsed in sterile Ringer's solution to eliminate any trace of the agent and transferred aseptically to a sterile tube. A segment of the vessel is taken at this moment for histologic studies and bacteriologic cultures for aerobes and anaerobes. If the segment is freeze-dried, the high vacuum in the system will eliminate all of the ethylene oxide and the rinsing process is not necessary.

Beta-Propiolactone. Chemical data.



* From Carbide & Carbon Chemical Corp., Passaic, N. J. also from Distillation Products Industries, Division of Eastman Kodak, Rochester, N. Y.

This substance is a viscous liquid with a specific gravity of 1.149, water soluble to the extent of 37 per cent by volume at 25 C. It is stable in concentrated form up to 10 months, when stored in refrigerator in sealed ampules.*

Toxicity: It hydrolyzes very rapidly to nontoxic compounds, although it itself is quite toxic. The degradation products of this compound are relatively nontoxic in the concentrations that are necessary here. At 37 C. its half-life is approximately 45 minutes. Avoidance of using concentrate solution in contact with the graft is of utmost importance because it is quite caustic.

Way of action: It reacts with hydroxyl, amino, carboxyl, sulfhydryl and phenolic groups, all associated with proteins.

Method of sterilization with beta-propiolactone: The vessel taken without sterile precautions is placed in a pyrex flask containing nonsterile:

Isotonic sodium chloride	200 cc.
Sodium carbonate (0.2 molar)	3.36 Gm.
Phenol red	10 mg.

To the flask is now added, slowly and with vigorous stirring at room temperature, 20 cc. of 10 per cent solution of beta-propiolactone made by adding 0.88 Gm of beta-propiolactone to 100 cc. of distilled water at 4 C. which must be maintained under constant refrigeration in order to minimize hydrolysis.

The flask is placed in water bath for two hours. At the end of this time, the graft is washed in a 0.2 molar phosphate buffer (pH 7.4) and transferred to a storage flask, after taking specimens for pathologic and bacteriologic studies. As the compounds formed after hydrolysis of beta-propiolactone are strongly acid, care must be taken to check the pH of the solution through the phenol red indicator during the sterilizing period. The fact that the degradation products have no appreciable action upon the tissues is a safeguard on the overaction of the drug which is not the case with ethylene oxide.

Following either of the above methods of sterilization, the grafts are now ready for storage either by the quick freezing method or the freeze-drying technic.

Physical Agents

High intensity electrons and gamma-ray irradiation are two physical methods for the sterilization of blood vessel grafts which have been demonstrated, both clinically and experimentally, to be satisfactory.

Sterilization by High-Voltage Cathode-Ray Irradiation. A high voltage cathode ray machine, such as the one constructed by Dr. Trump at the Massachusetts Institute of Technology, is necessary.

The segment of artery which has been taken without sterile precautions is placed in a plastic bag made of polyethylene film, sealed by heat at its ends, and is frozen in dry ice. When convenient, (days or weeks later) the grafts are sterilized by placing on a moving belt which carries the frozen packages through a beam of electrons 4 cm. in width, with a total irradiation of 2.5 million Roentgen equivalent physical units (R.E.P.).

In centers where high-voltage cathode-ray machines of 3 million volts or more are available, this method seems to be useful and simple. It is important to emphasize that this procedure produces drastic alterations of the irradiated tissues unless they are in a frozen state during the entire period of irradiation. After sterilization, the vessels can be maintained frozen in dry ice for long periods of time.

Sterilization by Gamma-Ray Irradiation. In the recent studies made by Carlson and coworkers, the source of gamma-rays was a tube of cobalt metal 13.5 inches long, 2.3 inches outside diameter and 1.7 inches inside diameter. Gamma-ray irradiation has a bactericidal effect and, at higher doses, also destroys tissue.

The use of cobalt^{60} tubes and the irradiation of vessels, taken without sterile precautions, with 2 to 3 million Roentgen Equivalent Physical units have proven to be satisfactory in its bactericidal action. It presents the advantage, over the previous method, of being less ex-

* B. F. Goodrich Chemical Co., Cleveland, O.

pensive and easier for transportation. The half-life of the cobalt[60] is 5.3 years.*

Preservation of Vascular Grafts

The arterial and vein segments obtained under sterile precautions or after sterilization by one of the recommended methods, are now ready for preservation. Two methods which are satisfactory and are relatively simple will be described. Further studies are being made to improve upon these and other technics of preservation.

Preservation by Quick-Freezing

Principle. As demonstrated by Tammann (1898), living matter can be frozen in the amorphous state by very rapid cooling, thus preventing fundamental cell damage of crystallization that occurs in slowly cooled material.

Technic. Grafts taken under sterile precautions or sterilized with beta-propiolactone or high voltage cathode ray irradiation are placed in sterile empty pyrex tubes with rubber stoppers and are rapidly immersed in a mixture of equal parts of dry ice and alcohol (−75 C.) or acetone (−78 C.) for 15 minutes and then placed for storage in a deep freezer until the moment of utilization (see preparation of grafts). If the grafts are kept in envelopes of plastic film, they are then frozen in the same containers to avoid further manipulation. Current opinion is that these grafts can be maintained for a period of at least one year. Whether this period can be extended is still to be determined. Sterilization in beta-propiolactone and quick-freezing seems to be one of the most practical methods for preservation of vascular grafts in small hospitals.

Preservation by Freeze-Drying

Principle. Passage from the frozen state to gas, i.e., sublimation, does not denature the proteins of a tissue if this takes place below a critical temperature which is specific for each protein. Thus, it is possible to store tissues, with preservation of normal histologic structure, in a desiccated state at room temperature, if the water is removed by sublimation. As the rate of drying is in direct proportion to the rate at which heat can be applied to the specimen, all factors being constant, the speed of the drying cycle depends on the maximum temperature at which the tissues can be processed (Clayperon equation). This is determined by its eutectic point which, in the case of blood vessels being below the freezing point, is necessarily long.

A freeze-drying unit consists basically of four elements:

(1) A vacuum system generally accomplished by the use of a mechanical oil-sealed rotary pump with or without the attachment of an oil diffusion pump to augment the vacuum.

(2) A manifold connection to attach the flasks containing the frozen material to be processed.

(3) A condenser or cold trap, kept cold by an external coolant, connected between (1) and (2) to prevent water vapors from reaching the vacuum system which reduces greatly its efficiency.

(4) A vacuum gage (McLeod, Pirani or Phillips type) to measure the pressures in the system.

Based on these principles, there are several types of apparatus available on the market and further work is being done in order to simplify them. The model described by Hufnagel, Rabil, and Reed (1954) has proven to be efficient and easy to operate.*

Technic. The specimens are frozen in the dry ice-acetone mixture, the container is connected to the system and the mechanical vacuum pump is started. If the vessels have been sterilized with ethylene oxide which freezes at −111.3 C., liquid nitrogen must be used to cool the condenser and to solidify the sublimated ethylene oxide.

If other methods of sterilization are used, the dry ice-acetone mixture has been shown to be sufficient. It is convenient to keep the

* Abbott Radioactive Pharmaceuticals (after fullment of regulations established by the Isotope Division of the Atomic Energy Commission, Oak Ridge, Tenn.)

* Biological Vacuum, Arlington, Va.

specimens frozen with dry ice-acetone during the early period of processing.

When all the air has been evacuated from the system, the vapor pressure of the tissue water closely approximates the total pressure of the system and becomes an index of its temperature, which will assume the temperature of the environment only after the process of sublimation is over, which usually takes from 6 to 10 hours at a pressure of 1 to 0.5 microns. To achieve such a pressure, careful avoidance of any leaks within the system is indispensable. There are two types of leaks: "virtual" and "actual"; the virtual ones are due to the presence of foreign substances whose vapor pressure is higher than the desired vacuum and can be eliminated by careful cleaning of the entire system. On the contrary, actual leaks must be found by the use of a high frequency coil and then closed with high vacuum seal.

Sealing of large diameter pyrex tubes is difficult and details for the sealing technic must be obtained from the manufacturers of each freeze-drying apparatus. Periodic control of the vacuum by the use of the high frequency coil is necessary, and all specimens that have lost their vacuum must be discarded. It is the general opinion that freeze-dried grafts, maintained under proper vacuum, can be stored indefinitely but an arbitrary period of two years is recommended for clinical use.

Other Methods

Since the pioneer work of Guthrie in 1912, numerous attempts have been made to utilize vascular grafts taken without sterile precautions and fixed with chemical fixatives. Clinical use of arterial homografts preserved in formalin has been reported; experimental work carried out by Peirce and associates with aortic segments fixed in 4 per cent neutral formalin has shown, however, that formalized grafts do not do as well as those preserved by other methods. Reports come from Japan indicating that 70 per cent alcohol is an excellent sterilizing agent and fixative because of its simplicity.

Preparation of Material before Implantation

Material Preserved by Quick-Freezing. The specimens that had been transported from the Bank in dry ice are rapidly thawed by immersing the containing flask in a water bath maintained at 35 C. for 10 minutes. After cleansing the rubber top of the pyrex flask with an antiseptic, the specimen is removed from the flask with sterile precautions and placed in a kidney basin, containing Ringer's solution 500 ml., dihydrostreptomycin 100 mg., penicillin "G" 100,000 units and heparin 50 mg. Antibiotics are used to increase the safety of manipulation and the heparin to lessen the possibility of thrombosis during implantation.

All branches are carefully ligated with transfixion sutures of no. 5 zero silk on an atraumatic needle. It is useful to test the graft for any possible leakage with a 20 ml. syringe and the above mentioned solution, being extremely careful to avoid any damage to the intima of the graft.

Freeze-Dried Grafts. The vacuum sealed tubes are immersed in Bard-Parker Germicide* or in 5 per cent iodine solution at room temperature for 30 minutes and then the end of the tube, distal to the graft, is opened with a sterile file. The specimen is removed and placed in a kidney basin with saline solution at room temperature for reconstitution. This process usually takes from 30 to 45 minutes depending upon the size of the specimen. It is important to avoid any manipulation during this period as the vascular wall is easily fractured in this state. After reconstitution, the vessel resembles the fresh graft prior to lyophilization. It is now handled in a similar fashion as the graft described in the preceding paragraph.

Histologic and Bacteriologic Controls

Specimens taken immediately after procurement with sterile precautions, or after sterilization by any other method described above, are used for microscopic studies and cultures. As previously mentioned, a circular segment of the upper abdominal aorta at the level of the celiac axis is usually studied. It is convenient to have, at the same time, a segment of the ascending part of the arch of the aorta for control. The specimen is rinsed in sterile saline which is used to inoculate routine bacteriologic cul-

* Bard-Parker Sol., A. E. Aloe Co., St. Louis, Mo.

tures for aerobes and anaerobes, as well as the samples taken from the pleural cavity of the donor during procurement under sterile precautions.

The cultures are observed up to a week after inoculation; the most common contaminants being *Staphylococcus aureus*, *Streptococcus alpha*, *Bacillus coli* and *Cl. welchii* as well as fungi. All contaminated material must be discarded. It is advisable not to sterilize the vessels for a second time, as the action of chemical agents, in particular ethylene oxide, have been shown to produce extensive damage to the arterial wall by prolonged immersion.

Although it is not absolutely essential to carry out histologic studies in the practical management of a blood vessel bank, ideally such studies are desirable as they are the only method of evaluating grafts prior to implantation.

The pathologic studies are carried out by fixation of arterial segments in 10 per cent formalin-Ringer's solution. Frozen sections are made and stained with Sudan black B which reveals fat and deposition of complex lipids. Other segments are imbedded in paraffin for routine staining with hematoxylin-eosin, Vorhoeff's stain for elastic fibers and Masson's trichrome stain for smooth muscle cells and connective tissue.

Since rupture and dislocation of elastic fibers of the media have proven to be the main reason for failure of aortic homografts, a careful study of the elastic fibers is made. Fat deposition in the subintima and atherosclerotic plaques are reasons for discarding the vessels. It is difficult at the present time to give exact criteria for histologic selection of the most suitable specimens. It is advisable, however, to utilize only those with a normal histologic picture and with well-preserved elastic fibers and relatively small amounts of fat in the intima and subintima.

Rigid and Flexible Plastic Prostheses

The difficulties of procurement and preservation of vascular grafts in small communities have led to an increased interest in the replacement of vascular segments by nonbiologic products, which could be easily prepared to any required shape or size. The human recipient's reaction to these prostheses, constructed from several different materials, is still unknown over long periods of time. Early results seem, however, satisfactory when employed under proper conditions. The prosthesis may be classified into two groups: rigid and flexible.

Rigid Prostheses

Of many different materials that have been utilized in the construction of plastic tubes, methyl-methacrylate (Lucite*) has been one which has yielded the best results.

One of us (C. H.) has summarized the necessary criteria for the selection of rigid plastic prostheses as follows:

(1) The material employed should be relatively biologically inert.

(2) It should have adequate strength.

(3) It must resist clotting.

(4) The internal surface of the prosthesis must be extremely smooth.

(5) The junction between the vessel and the prosthesis must also be extremely smooth.

(6) The anastomosis between the tube and the vessel must be effected by a method which does not produce necrosis of the arterial wall at the point of junction. Tubes made out of methyl-methacrylate and anastomosed with rings made of Nylon with fixation by multiple point pressure on the circumference of the arterial wall, thus avoiding circumferential pressure, have been satisfactory in selected locations, as the aorta, where the variation in diameter of its different segments is relatively slight. There are two main difficulties in the use of rigid prostheses: (a) Because of the rigidity of the tube, it is impractical where there is flexion of the vessel or where there are branches of variable size, shape and angulation. (b) As there must be a close approximation between the size of the prosthesis to the vessel above and below, a large selection of tubes of different diameters and lengths must be available.

(7) The potential "cul de sac" which is present between the fixation ring and the end

* DuPont de Nemours & Co., Wilmington, Del.

of the prosthesis should be obliterated to prevent thrombosis.

Flexible Prostheses

Because of the limitation of rigid types of plastic prostheses, many flexible materials have been used beginning with the work of Voorhees, Jaretzki, and Blakemore with Vinyon "N" cloth. Several materials have been successfully implanted in man.

(1) Vinyon "N" cloth, 27 denier, 144 by 90 strands per square inch.*
(2) Woven Nylon, 241 F, 277 by 240 strands per square inch.†
(3) Orlon 81 fiber, 75 by 100, or 100 by 100 weave (Hufnagel).‡
(4) Dacron cloth.§

Preparation of Flexible Plastic Prostheses

The tubes are constructed by sewing the fabric, preferably on a sewing machine, with the same thread of which the fabric is made and with a very fine needle (no. 8, Singer). Straight tubes and branched tubes are made, including Y bifurcations of different lengths and diameters, flaring the ends slightly in order to make a cuff. Seamless tubes and some of the new types of cloths are now being studied.‖

Prefabricated Nylon tubes were recently devised by Sterling Edwards. A portion of the tubes is crimped in order to permit flexibility where the defect in an artery is adjacent to a joint. However, at the present time the tube does not have longitudinal stretch. It is joined to the end of the artery by the usual method of arterial suture. A number of successful clinical cases have been described.

Due to present difficulties in obtaining fabrics with known biologic action in the recipient, it is important to immerse the cloth in a jar with 10 per cent aqueous solution of a detergent¶ for 12 hours in order to eliminate oil and foreign matter which accumulates during processing. The cloth should be rinsed at least three times in distilled water or saline.

For sterilization, each particular fabric must be handled individually in respect to the method used. Orlon type material and Dacron should be autoclaved. Nylon and Vinyon "N" on the contrary, must be sterilized by boiling for 10 to 15 minutes.

Surgical Considerations

The prosthesis is sutured to the blood vessel by the usual method of arterial anastomosis with an over and over suture which, in the instance of arteriosclerotic vessels, is preferable to an everting mattress suture. The needle should pass from the outside of the prosthesis to the lumen and then through the artery from inside out in order to maintain apposition of the intima to the media of the sclerotic vessel.

After the prosthesis has been placed and the blood allowed to enter the tube, some bleeding may occur, depending on the type of cloth that is used. Voorhees and Blakemore have avoided this difficulty with Vinyon "N" by preclotting the tube, using the recipient's blood so that fibrin would be deposited in the interstices of the cloth and prevent excessive bleeding. It is important to express all of the clot from the lumen of the tube before implantation.

In general, all these prostheses are more difficult to suture than arterial homografts, because of absence of elasticity of the cloth. At the present time, diagonal weaves are being studied in order to increase the elasticity of these fabrics.

The prosthesis should be fitted precisely to the defect because additional length will result in buckling and thrombosis. If more than three anastomoses must be performed then the use of a prosthesis may be associated with serious difficulties.

Summary

Recent advances in the diagnosis and treatment of segmental lesions of large blood vessels have created a need for storage of arterial and venous grafts and plastic prostheses. It has been the purpose of this paper to describe in some detail the problems and technics of procurement, sterilization, preservation and util-

* Union Carbon and Carbide Co., New York, N. Y.
† Stehli Co., Inc., New York, N. Y.
‡ Cadillac Textiles, New York, N. Y.
§ A. Lamport and Bros., New York, N. Y.
‖ C. P. Braining Corp. Central Valley, N. Y.
¶ Alconox-Wetting Agent, Alconox, Inc., Jersey City N. J.

ization of arterial and venous grafts. Emphasis has been placed on the need for bacteriologic and histologic safeguards in the maintenance of a blood vessel bank. A brief section was devoted to the current status of plastic prostheses.

Finally, it is of considerable importance to recognize the fact that this is a new field which is being subjected to intensive study and that advances and modifications will be forthcoming. Therefore, this paper represents an interim rather than a final report.

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SUMMARIO IN INTERLINGUA

Progressos recente in diagnose e tractamento de lesiones segmental del major vasos sanguinee ha resultate in le necessitate de immagazinar graffos arterial e venose e prostheses plastic. Le objectivo del presente articulo es describer in detalio le problemas e technicas del procuration, sterilisation, preservation, e utilisation de graffos arterial e venose. Es sublineate le necessitate de mesuras protective bacteriologic e histologic in le mantenentia de un banca de vasos sanguinee. Un breve section del articulo es dedicate al stato currente del prostheses plastic.

Finalmente, il es del plus alte importantia recognoscer que il se tracta hic de un nove campo que es le objecto de intense studios de maniera que progressos e modificationes es a expectar. Consequentemente le presente articulo es un reporto interime plus tosto que final.

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CLINICAL PROGRESS

Recent Advances in the Investigation and Management of Cerebrovascular Disease

By JAMES PETER MURPHY, M.D.

CEREBROVASCULAR ACCIDENTS represent the third most common cause of nontraumatic death in the United States of America. More patients are admitted to hospital wards with major brain stroke than with any other neurologic disorder. Fortunately, recent advances in our knowledge of the embryology, anatomy and physiology of the cerebral circulation are improving methods of diagnosis and treatment of cerebrovascular disease.

EMBRYOLOGY

Probably because of better recognition, cerebrovascular accidents due to rupture of congenital aneurysms of the circle of Willis or of arteriovenous malformations of the brain are far more numerous today than 20 years ago. In a series of 200 patients with cerebrovascular disorders analyzed by Brain,[4] 16 per cent harbored aneurysms or congenital angiomas. Reinvestigation of the embryologic construction of the intracranial vascular circulation by Padget[26] and others has disclosed the *raison d'être* of these developmental anomalies.

Faults in the media of arteries, particularly at the points of their bifurcation, failure of complete resorption of primitive vessels of phylogenetic but not ontogenetic importance, inadequate fusion or anastomosis of the carotid and vertebral circulations and incomplete splitting of the three vascular layers (cranial, meningeal and cerebral) of the embryonal head are largely responsible for the presence of intracranial circulatory malformations in adult life. Acquired factors such as arteriosclerotic weakening of the internal elastic lamina of arteries and focal necrosis of vessels during angiitis contribute to aneurysmal sacculation and rupture[14] which is manifest most often in maturity and not in infancy.

ANATOMY

Collateral Arterial Circulation: Few vessels of the cerebrum and cerebellum are true end-arteries. Unfortunately, these lie in the critical fields of supply of the basal ganglia and internal capsule, pons and the tip of the temporal lobe. Collateral anastomoses are numerous, especially superficially,[36] and increase numerically with age. At autopsy of elderly individuals, occlusion of major vessels such as the middle cerebral artery have been found without infarction, peripheral to the site of thrombosis.

Anastomoses between the carotid and vertebral circulations are quite variable, a "normal" circle of Willis being found in only 50 per cent of brains examined. Only thus can hemiplegia, following unilateral carotid thrombosis in one patient, be reconciled with bilateral occlusion of both carotid arteries (verified by angiography) without clinical aftermath in others. External-internal carotid cross circulation is not a negligible factor in preserving intracranial circulation, as demonstrated by angiographic filling of the cerebral vessels via the ophthalmic artery after complete occlusion of the internal carotid.

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Microscopic Structure of Cerebral Arteries. The intracranial arteries are characterized by a relatively thin muscularis media. That cerebral arteriospasm may occur clinically nonetheless is evident in migraine with neurologic complications (for example, hemianopia). Sympathetic vasomotor fibers have been traced peripherally to arterioles of 50 micra caliber. The intact internal elastic lamella is of greater importance in maintaining arterial integrity than the thin medial coat and almost nonexistent adventitia. Only when the thick protective elastic membrane, deficient congenitally or weakened by sclerosing disease perforates, can cerebral hemorrahge occur.

Intracranial Veins and Dural Venous Sinuses. Intracranial venous anastomoses are numerous. Angiograms in cases of major cerebral venous occlusive disease disclose that the anastomotic vein of Labbé and the basal vein of Rosenthal are capable of conducting the principal aliquot of blood from one hemisphere to the ipsilateral transverse sinus.[21] Gradual complete obliteration of the superior sagittal sinus or of one transverse sinus can be compensated for by collateral drainage. In a patient with probable sagittal sinus thrombosis and papilledema upon whom I performed a subtemporal decompression after normal ventriculography, the eyegrounds and vision were perfect within six weeks. This is a not uncommon experience in the surgical treatment of "pseudotumor cerebri." Conversely, acute compression of the superior longitudinal (sagittal) sinus, by depressed fracture of the vertex of the skull, results in severely increased intracranial pressure.

The role of the vertebral venous plexus, anastomotic with the intracranial drainage through occipital and suboccipital emissary veins, is not negligible in compensating for venous thrombosis within the skull. Indeed, both internal and external jugular veins have been sacrificed during radical neck dissections for cancer with no more than temporary increase of intracranial pressure. The vertebral venous plexus conducts all blood from the head to the heart under these circumstances.

Physiology

The objective measurement by Kety[19] and others of the rate and extent of cerebral flow of blood has been a great advance. Average normal cerebral blood flow is 54 to 65 cc. per minute per 100 Gm. of brain. The highest value recorded was 164 cc. per minute per 100 Gm. of brain in a patient with an arteriovenous anomaly; the lowest flow was 22 cc. per minute in a patient with polycythemia vera. With uncomplicated essential hypertension, cerebral blood flow and cerebral metabolic rate are normal; cerebrovascular resistance is increased. When hypertension and cerebral arteriosclerosis coexist, cerebral blood flow and brain metabolism are both reduced. Although carbon dioxide inhalation in patients with cerebral arteriosclerosis alone does not increase cerebral flow, when both hypertension and arteriosclerosis are present, an increase of almost 20 per cent in cerebral blood flow occurs during administration of carbon dioxide.[29] Aging as such is associated with decreased cerebral blood flow and reduced oxygen uptake by the brain.

Drug Therapy. Caffeine and aminophylline reduce cerebral blood flow measured by the nitrous oxide technic, paradoxically, in view of the common dependence upon morning coffee for wakefulness and the undoubted value of aminophylline in treatment of some patients with a recent stroke. Priscoline does not increase total cerebral blood circulation, whereas intravenous papaverine does. Histamine, nicotinic acid and the nitrates are capable of enlarging the intracranial vascular bed, as verified by experimental observation, but only if the systemic blood pressure does not fall excessively.

Hypotension. The preceding observation applies particularly to the use of sympathetic ganglion blocking agents. Hexamethonium in particular is condemned in clinical practice; general hypotension results in marked reduction of cerebral blood flow and cerebral ischemia in elderly hypertensive patients.[8] On the other hand, a hexamethonium-induced fall of blood pressure in animals results in dilatation of pial arteries, the "agonal phenomenon" of

Forbes. This may apply clinically to healthy young people in shock but not to the elderly, incapable of such a response.

Further investigation of induced hypotension assisting major surgery has revealed it to be a two-edged sword. If sclerosis of brain arteries exists, the procedure may be dangerous even though pressures in the brachial and carotid arteries have been found to be equal in the prone position. Unless compensatory mechanisms in the brain or its circulation accomplish increased extraction of oxygen from circulating blood, traumatic or artificial shock may become lethal, probably because of intracerebral hypostatic infarction. The electroencephalogram may be a sensitive indicator of disordered cerebral function occurring during surgical hypotension.

Clinical Syndromes

Cerebral Vasospasm

The concept of cerebral arteriospasm is controversial. It should be pointed out that every patient suffering from migraine who sustains transient hemianopia, aphasia or hemiplegia is probably experiencing temporary spasm of the posterior cerebral or middle cerebral arteries. Intracranial arteriospasm has been observed by neurologic surgeons operating upon the circle of Willis. Likewise, definite and persistent angiospasm, following embolization of cerebral arteries or induction of hypertension in experimental animals, has been observed through skull windows. The possible benefit of vasodilating drugs or of stellate block in patients with evanescent "strokes" should not be withheld.

Cerebral Infarction

Intracranial angiography and pathologic examinations have made it increasingly apparent that nonhemorrhagic and nonembolic cerebral accidents are not necessarily the result of true thrombosis, but are often the effect of infarction without thrombosis. In over 60 per cent of cerebral infarcts studied at autopsy, no intra-arterial thrombus can be found. Contrariwise, occluded arteries may be discovered without peripheral infarction. In the remainder of cases, thrombosis of a major vessel without adequate collateral circulation results in infarction of the brain.

Infarction without Thrombosis: Many nonhemorrhagic, nonembolic and nonthrombotic infarcts occur during sleep or when hypotension develops from another cause. Arteriosclerotic narrowing of the internal carotid or cerebral arteries and the absence of potentially functioning anastomoses are important contributory factors. Ecker[7] has observed arteriospasm in 90 per cent of patients with stroke, hemorrhagic or otherwise. Anger or hostility may induce vascular spasm sufficient to occlude an already narrowed vessel.

Cerebral Infarction in Heart Disease: Heart failure is frequently an instigating or complicating factor in cerebral infarction. The simultaneous occurrence of infarcts in the heart (coronary occlusion) and brain is not uncommon. Brain damage in the cerebrocardiovascular syndrome is often nonthrombotic, although Scheinker[28] has reported the occurrence of true thrombosis of small cortical veins during chronic heart failure. This latter complication may be responsible for mental disturbance, hemiplegia or epileptic seizures in the decompensated cardiac patient.

The "Little Strokes:" Alvarez[1] has stressed the clinical significance of a common finding in the routine autopsy examination of the brains of the elderly, long familiar to every neuropathologist, that is, multiple small cystic infarcts in the pons, mesencephalon, basal ganglia and thalami. These lesions are due to the combined effect of arteriosclerosis and brief but significant hypotension.

Diverse clinical syndromes, related in their fundamental pathologic substrate to "little strokes," are listed by Alvarez: (1) Episodes in chronic illness misdiagnosed as "nephritis," "abdominal upsets" and the like, in which "death keeps taking little bites" of the patient; (2) vague mental changes, particularly of memory; (3) loss of working ability; (4) premature aging, general "slowing-up" and carelessness; (5) fear of being alone; (6) loss of old interests and of joy in life; (7) poorly

localized but severe pains in the chest or abdomen; (8) "acute indigestion," diarrhea or incontinence and (9) burning of the tongue or "bad taste in the mouth." To these may be added (10) so-called "Menière's syndrome" which is often a manifestation of infarction in the pons in the older patient, especially if there is loss of sensation of the face and (11) a group of disorders representing a cumulative effect, predominantly upon the motor system, of multiple and repeated infarcts in the brain stem–"arterio-sclerotic rigidity" of Foerster, pseudobulbar palsy, atypical Parkinsonism and the syndrome of "*démarche à petit pas*".

Thrombosis of the Posterior Inferior Cerebellar Artery. The Wallenberg syndrome, the result of occlusion of the posterior inferior cerebellar artery or of the anterior inferior cerebellar artery (Foix) is selected for special comment from a host of specific intracranial arterial syndromes. It appears to be increasing in incidence among the younger age group. Angiographic studies reveal that the parent vertebral artery at the base of the skull may be thrombosed instead of the cerebellar vessels.[20] When the syndrome appears in a 20 to 30 year old patient, hypoplasia of one posterior inferior cerebellar artery may be responsible for occlusion rather than arteriosclerosis. It is interesting that when thrombosis has actually occurred in the vertebral artery, the brain stem is capable of withstanding more ischemia than thought possible, since most patients with the Wallenberg syndrome recover fairly promptly, although not necessarily completely.

Carotid Thrombosis. Thrombosis in the cervical carotid artery with consequent intracerebral infarction is a subject of current clinical interest. The discovered incidence of cervical carotid thrombosis in angiograms, performed on patients with cerebrovascular disorder, is one to two per cent.[10] The clinical significance of this observation is tempered by the observation that cerebral infarcts occur in only one-third of patients with carotid thrombosis,[16] owing to adequate collateral supply of the ipsilateral cerebral hemisphere through the circle of Willis or via external-internal carotid anastomoses.

When impairment of brain function does occur, three clinical syndromes are possible[18]: (1) transient attacks of hemiplegia, (2) slow progression of hemiparesis, aphasia, etc., featured by severe headache and convulsions or (3) sudden, catastrophic infarction with coma, hemiplegia and loss of speech. Diagnosis is often difficult on clinical grounds alone. Angiography proves the existence of thrombosis of the common carotid artery below the carotid sinus or of the internal carotid artery just above the carotid bifurcation or in the carotid syphon. Without angiography, the diagnosis may be suspected or established by inability to palpate the pulse of the internal carotid normally felt in the posterolateral pharynx, or by the induction of immediate unconsciousness when the opposite carotid is occluded by manual pressure on the neck.

The treatment of carotid thrombosis is unsatisfactory by any means. Fortunately, spontaneous recovery is frequent, due to development of collateral circulation to the cerebral hemisphere deprived of blood, assisted by vasodilator drugs. Restitution of function is usually not complete.

Cerebral Embolism

After major embolism of the brain, neurologic disability is severe and rapid, compared with the more gradual development of spontaneous cerebral infarction. Valvular or myocardial heart disease as the source of emboli is almost always present. A problem complicating mitral valvulotomy is embolism from atrial thrombi. Temporary compression of the innominate and common carotid arteries during surgery is recommended in prevention. Hemiplegia, due to cerebral embolism from a myocardial mural thrombus, may be the first clinical sign of an otherwise silent coronary artery occlusion. The middle cerebral arteries, particularly the left, are often blocked by large embolic masses. The prognosis for recovery after major cerebral embolism in rheumatic heart disease is guarded.[6]

Other Types of Cerebral Embolism. Fragmentation of clots deposited on the interior of the carotid sinus was recognized as a cause of cerebral embolism by Chiari in 1905. Air embolism has occurred frequently in patients

undergoing neurosurgical procedures in the sitting position. Fat embolism not uncommonly accompanies severe head injury, especially when an automobile accident has resulted in multiple fractures and soft tissue contusions, and can account for decerebrate rigidity and hyperpyrexia. The vertebral venous plexus, readily influenced in direction of flow by sudden changes in intracavitary pressure is a cardiac "by-pass" allowing metastasis of suppuration or malignancy from the lung to the brain.

Cerebral Hemorrhage

The frequency of hemorrhage into the brain as compared with the infrequency of apoplectic hemorrhage into other viscera remains unexplained. Anatomic peculiarities of the intracranial circulation are significant. The great importance of the internal elastic lamella in the walls of the cerebral arteries as contrasted with the lesser relative importance of this membrane in arteries elsewhere is undoubtedly a factor, as is the poverty of intracranial vascular adventitia.

The implication by Charcot and Bouchard (1868) of miliary aneurysms on small intrinsic arteries as a cause of cerebral hemorrhage is substantiated by modern embryologic and anatomic research which has disclosed the frequency of developmental aberrance of the circle of Willis and branches, particularly in the critical zone of the basal ganglia and internal capsule. Zimmerman[40] has emphasized the occurrence of dissecting aneurysms due to intramural rupture of a vas vasis in a sclerosed artery, which then perforates causing intracerebral hemorrhage. The hitherto unsuspected frequency of minute arteriovenous malformations in the basal forebrain circulation is a newly recognized cause of intracerebral hemorrhage in the young. The theory of Globus and Strauss,[12] based upon a previous opinion of Rouchoux (1844) that perivascular encephalomalacia surrounds an artery which is, therefore, more easily ruptured by increased intravascular tension, tends to be supported by experimental investigations.

Cerebral hemorrhage occurs almost exclusively in the hypertensive patient, barring the occasional intracerebral rupture of a large arterial aneurysm or small arteriovenous malformation in the normotensive individual. The most frequent site is the internal capsule. Sclerosing changes, accompanying but not necessarily due to the progress of hypertensive disease, destroy the internal elastic lamella of a small, intrinsic artery, perhaps congenitally weak at a point of bifurcation or of aneurysmal anomaly. When a sudden increase of already heightened intravascular tension occurs as during an emotional crisis, a dissecting aneurysm forms in the arteriosclerotic wall or a direct mural break ensues. Focal necrotic changes due to angiitis may be contributory. As arterial blood escapes into the surrounding brain, it tears a path along tissue planes in an anteroposterior direction. Veins are torn, contributing venous to arterial hemorrhage.

These events progress with lightning-like rapidity. The involved part of the brain swells rapidly, forcing the medial inferior aspect of the ipsilateral temporal lobe (hippocampal area) down through the incisura of the tentorium, compressing the midbrain against the opposite tentorial ridge. Secondary hemorrhages result in the midbrain and pons because of acute tamponade of the basal vein of Rosenthal and allied small vessels. Consequent mesencephalic damage accounts for the familiar pattern of decerebrate rigidity prior to death. Transection of the midbrain or perforation of hemorrhage into the ventricular system are the immediate causes of exitus. Hematemesis or gastromalacia are terminal events. Cerebral hemorrhage is never as immediately fatal as is lethal subarachnoid hemorrhage.

Subarachnoid Hemorrhage: Intracranial Aneurysm

The distinction between "cerebral hemorrhage" and "subarachnoid hemorrhage" is important clinically. "Cerebral hemorrhage" implies rupture of an artery not essentially aneurysmal in character directly into the substance of the brain, in a patient who is afflicted with hypertension and/or arteriosclerosis. "Subarachnoid hemorrhage" is the term applied generally to perforation of a congenital arterial aneurysm of the circle of Willis pri-

marily into the subarachnoid cisterns surrounding the base of the brain. Blood from a direct intracerebral hemorrhage can reach the ventricular or subarachnoid spaces almost as rapidly as that from hemorrhage into the basal cisterns. The initial degree of interior brain damage, revealed by hemiplegia or coma, may permit an etiologic distinction of the source of bleeding. To further confuse differential diagnosis, it is apparent statistically that patients, harboring congenital aneurysms of the circle of Willis, are subject to premature cerebral arteriosclerosis and hypertension and that an intracerebral clot frequently surrounds an aneurysmal sac that has ruptured. Moreover, aneurysms may rupture into the brains of the elderly, just as in the middle-aged or juvenile patients.

Therefore, the only logical approach to differential diagnosis of the intracranial hemorrhagic disorders is one based upon strict adherence to all etiologic and pathogenetic rules. The importance of such accuracy of diagnosis is practical therapeutically.

Pathologic Considerations. The researches of Padget, Forbus, Bremer and others emphasize the role of embryologic aberrancy or failure in the development of intracranial aneurysms. That the average time of rupture of aneurysms of the circle of Willis is in the mid-forties emphasizes the contributory effect of other disease processes. The destructive action of arteriosclerosis or of focal angiitis is immediately responsible for perforation of aneurysms.

Postmortem investigations of patients dying from subarachnoid hemorrhage have revealed: (1) The high incidence of multiple cerebral arterial aneurysms; (2) the frequency of associated vascular dysplasia (cerebral arteriovenous malformation, coarctation of the aorta, polycystic kidneys); (3) the premature development of cerebral arteriosclerosis; (4) a significant combination with cardiac disorders; (5) evidence of repeated bleeding episodes prior to death; (6) cerebral parenchymatous lesions in 50 per cent of fatal cases and (7) an almost invariably anomalous circle of Willis.[37]

Clinical Observations. It is remarkable how often massive subarachnoid hemorrhage in the elderly may not result in classical signs of meningeal irritation. Concerning medicolegal aspects of this disorder, a reply to a "Letter to the Editor", in the *Journal of the American Medical Association*, Jan. 29, 1955, states: "It may be postulated that if a person who had an intracranial aneurysm were to perform heavy physical exercise and possibly strain severely . . . enough alteration in intracranial tension to affect the thinned-out portion of an aneurysm might occur; rupture in this way might be associated with such activities. However, an exact cause-and-effect relationship would be very difficult to establish."

Prognosis. Subarachnoid hemorrhage accounts for 5 per cent of all cases of sudden death and is responsible for 25 per cent of fatalities due to disease of the nervous system. The mortality rate in first serious attacks varies from 30 to 50 per cent in different reported series and second significant ruptures are said to have a fatal incidence of 75 per cent. On the other hand, Hyland[17] declares that patients surviving an initial episode of subarachnoid bleeding have an 80 per cent chance of living indefinitely thereafter without fear of recurrence. Discrepancy in such prognostic predictions necessitates further statistical research. Mount,[24] collating the experience from many neurologic centers found that the mortality rate from subarachnoid hemorrhage was 48 per cent in patients treated medically and only 14 per cent in patients treated surgically, a strong argument for surgical intervention when possible.

Arteriovenous Malformation

The increasingly widespread use of angiography as a diagnostic technic has revealed a hitherto unsuspected frequency of arteriovenous malformation of the brain as an occasional cause of hydrocephalus in infancy, of stroke in childhood or adolescence and of epilepsy or of repeated minor or major subarachnoid hemorrhages at any age. Extensive studies have disclosed the prevalence in such patients of generalized angiomatosis, of which the Lindau-von Hippel disease is one type. Hemangiomatosis is transmitted as a mendelian

dominant gene, not sex-linked; it is one of few inherited neoplastic dyscrasias of man.[30]

Venous and Venous Sinus Disease

Angiography has also disclosed that many cases of increased intracranial pressure or of obscure bleeding, particularly in the puerperium, are due to thrombosis or thrombophlebitis of the dural venous sinuses or of the cerebral veins. Stevens[34] has pointed out the frequency with which cerebral venous occlusion causes puerperal hemiplegia, sometimes misdiagnosed as an eclamptic complication. He calls attention to the decreased blood clotting time in the last trimester of pregnancy and the increased incidence of thrombophlebitis elsewhere in the body at this time. Cerebral venograms have revealed extensive venous occlusions in such patients.[21]

Hypertensive Brain Disease

Experimental malignant hypertension has been studied by Byrom.[5] Cerebral attacks were precipitated in rats made hypertensive by the Goldblatt method when saline solution was substituted for drinking water. Pathologic examination revealed focal arterial necrosis, brain infarcts or hemorrhages in the majority of subjects. Cerebral water content was increased in encephalopathy but not in uncomplicated hypertension. Brain hydration was thought to be due to capillary leakage, secondary to the arterial spasm observed through skull windows. The point at which physiologic vasoconstriction as a response to heightened intravascular tension becomes uncontrolled focal spasm is said by Byrom to represent the dividing line between benign and malignant hypertension. Lowering of the blood pressure relieved intracranial angiospasm in his animals as it does in clinical patients, whereas cervical sympathectomy had no effect.

The concept of multiple "little strokes" as the explanation of chronic hypertensive cerebrovascular disease has been invoked by Hughes and co-workers.[15] Whereas an automatic intrinsic mechanism of unknown type permits normal cerebral metabolism in uncomplicated hypertensive disease, despite a mean increase in cerebral vascular resistance of 75 per cent, the development of hypotension is not accompanied by persistence of adequate oxygen consumption, which decreases as the blood pressure falls. The necessity for caution in the induction of hypotension during surgery on the hypertensive patient is apparent.[13]

Cerebral Arteriosclerosis

Extensive pathologic investigations of cerebral arteriosclerosis by Fisher[11] reveal that: (1) cerebral arterial atheromatosis parallels that found elsewhere in the body; (2) atherosclerosis of the brain is a focal process and tends to occur where vessels enter the skull, loop, branch or bifurcate; (3) hypotensive vascular collapse, embolic phenomena or true thrombosis must also eventuate before cerebral arteriosclerosis can be responsible even in part for neurologic symptoms or signs; (4) collateral circulation may permit the occlusion of even large arteries without infarctive sequelae; (5) barring significant narrowing or thrombosis of one or both carotid arteries, arteriosclerosis per se is not a cause of senile dementia. Capillary fibrosis is found in 86 per cent of aged patients with normal mentality. Parkinsonism in old age cannot be explained as a result of arteriosclerosis alone.

"Cerebral Vascular Insufficiency." Functional inadequacy of the intracranial circulation may account for transient neurologic episodes in the known or suspected presence of arterial disease. Hypotension or other unknown factors often are contributory. Arteriosclerotic insufficiency of circulation through the basilar artery is particularly common in the elderly patient. The numerous and tiny arterial derivatives supplying the all-important brain stem are easily deprived of blood, temporarily or permanently, with the familiar effects of "dizziness," "fainting," comatose attacks, transient or persistent tetraplegia or quadraplegia, "Menière's syndrome," diplopia or temporary blindness.

Inflammatory Collagen Diseases

Cerebral venous thrombophlebitis can develop in the young patient as a manifestation

of a rheumatic diathesis or as the result of transient bacteremia. The syndrome of preceding malaise, a sudden convulsive attack which is followed by fever, hemiplegia, aphasia or confusion is the characteristic clinical manifestation of thrombophlebitis of the brain. Spinal fluid examination reveals slightly increased pressure, excess of protein content and of cells. Venous rather than arterial involvement is suggested by the usually benign nature of the process.

Collagen vascular disease is accompanied by intracranial complications. One of the major causes of death from lupus erythematosus disseminatus is cerebral angiitis. Cerebral vascular involvement in serum disease and in supposedly benign temporal or cranial arteritis is not uncommon. Periarteritis nodosa involves the brain in 10 per cent of cases. In all these disorders small blood vessels are implicated.

Migraine

The familiar scintillating scotomata and homonymous hemianopsia often precede or accompany an attack of unilateral headache and are probably due to spasm of the ophthalmic or posterior cerebral arteries which is usually reversible. Permanent brain damage may result, however, from migraine. In one of my patients, cerebral infarction was found at operation to be the effect of vasospasm during a severe migrainous seizure.[25] Wolff and associates[38] have observed spontaneous hematomas and effusions in the temporal muscles of certain migraine patients during episodes of headache. The frequency of abnormal electroencephalograms in this condition may be, in part, the aftermath of ischemic cerebral changes.

Diagnostic Studies

Spinal Puncture. The problem of whether or not blood withdrawn with spinal fluid via lumbar puncture is of previous origin or is due to trauma during spinal tap has recently been resolved by Matthews and Frommeyer.[22] These investigators, studying blood in cerebrospinal fluid in vivo and in vitro have concluded that crenation of red blood cells occurs immediately in either media and is of no clinical assistance. Only the presence of "ghost cells" (envelopes of erythrocytes) and xanthochromia definitely prove the existence of subarachnoid or intraventricular hemorrhage prior to spinal puncture.

Intracranial Air Studies. The "small encephalogram" of Monrad-Krohn is much better tolerated by the patient with cerebrovascular disease than is total spinal fluid replacement. Adequate roentgenographic visualization of the ventricular system is often possible when only 25 to 30 cc. of air are injected through the spinal route, the patient sitting upright. Local anesthesia is sufficient, as the procedure is not painful. It is important to inject 10 to 15 cc. of air before spinal fluid is withdrawn; gas is more likely to be introduced into the ventricles in this manner and dangerous intracranial herniations are avoided. Ventriculography has been superseded largely by angiographic examination of patients with cerebrovascular disorders.

Intracranial Angiography. Cerebral angiography is the neuroradiologic technic suited most ideally to the differential diagnosis of intracranial vascular disease, since the blood vessels of the brain are visualized directly only when injected with a radiopaque contrast medium. The carotid and vertebral arteries may be cannulated either after surgical exposure of the vessels or better and most usually by the percutaneous method. Serial x-ray films taken during the progress of injection reveal first intracranial arteries and then veins; by rapid and multiple exposures, any phase of the cerebral vascular cycle may be demonstrated. Arterial aneurysms and arteriovenous malformations fill and are revealed in size, location and origin; displacement of arteries and veins from their normal positions denote intracranial mass lesions such as hematomas or areas of infarction. Poverty and angulation of arteries confirm an arteriosclerotic condition and failure of visualization of major vessels beyond points of occlusion proves the existence of intravascular thrombosis or embolism.

Many more carotid angiograms are performed than injections of the vertebral artery,

since the majority of accessible and treatable vascular lesions of the brain lie above the tentorium. Vertebral angiography is a more difficult and hazardous technic than is carotid angiography and the revelation of pathologic alteration of the blood vessels of the brain stem is often only of academic interest. Although principal diagnostic emphasis has been placed upon arteriography of the brain, an increasing number of reports concerning the value of venography is appearing in literature. One procedure described accomplishes filling of cerebral venous sinuses and veins via diploetic connections through the bone marrow of the skull. Injection of contrast medium into the exposed superior longitudinal sinus is the only method of proof of occlusion of this important vessel.

Thorotrast, a radioactive substance excellently radiopaque, has been abandoned for use in percutaneous cerebral angiography, since leakage of material from the site of injection results in a painful, disabling and even lethal granulomatous cicatrix in the neck. Diodrast is the contrast medium universally employed at present; a 35 per cent concentration is the limit of tolerance by the cerebral vessels and even this strength is productive of an unpredictable degree of intracranial angiospasm. Iodine sensitivity should be ruled out beforehand and papaverine is administered intravenously, just before injection of diodrast, to prevent the arterial spasm which can and has caused hemiplegia or another untoward reaction.

Intracranial angiography is a procedure not to be undertaken lightly. It is indicated when possible surgery after subarachnoid hemorrhage requires a precise diagnosis, when the effects of arterial occlusion are otherwise indistinguishable from those of intracranial tumor and for exact localization of expansile intracranial lesions. Vascular contrast studies are precluded when differential distinction is only academic, when the patient is extremely old, is in an advanced state of arteriosclerosis or hypertension, in heart failure, uremia or has obviously had a recent severe infarctive stroke.

Electroencephalography. Although far from infallible, the electroencephalogram is of value in the differential diagnosis and management of vascular disorders of the brain and is an examination which is painless, convenient and may be readily repeated. Studying patients with hypertensive disease, Roberts and Walker[27] found that the electroencephalogram was abnormal even without evidence of brain damage in over 50 per cent of cases. When neurologic signs other than epilepsy were present, the electroencephalograph test was abnormal in at least 80 per cent. When convulsive disorders resulted, all patients manifested significant electroencephalographic changes. Epilepsy is a not uncommon aftermath of cerebrovascular accident.

Residual electroencephalographic abnormalities following cerebral infarction are common in the ipsilateral temporal area. Relatively constant production of irregular slow waves tends to distinguish infarction from infiltrative malignant neoplasm which usually produces high voltage delta activity in bursts. Minor irregular and slow spike activity from the anterior temporal leads is a frequent finding in elderly patients and is probably the result of small infarctions in the tip of the temporal lobe, the hippocampal portion of which is supplied by an end-artery.

Therapy

Cerebral Vasospasm. If one assumes that intracranial arteriospasm is responsible for certain cerebrovascular accidents or their complications and that sympathetic nervous influences may perpetrate deleterious angiospastic effects, it seems logical to suppose that stellate nerve block, with temporary paralysis of the intracranial autonomic sympathetic inflow would be of value in such cases. There is no subject of greater neurologic debate at present. At one extreme are enthusiastic adherents of the procedure who claim benefit in all types of nonhemorrhagic stroke after stellate block. At the other extreme are those who deny that intracranial arteriospasm ever occurs, who negate the possible operation of sympathetic innervation in regulation of cerebral blood flow under even emergency conditions and who even claim that the patient with an

infarctive brain lesion is made worse by the procedure.[32]

Stellate block can do no more than relieve vasospasm of major arteries or of small vessels on the periphery of a small infarctive lesion of the brain. This arterial spasm may be of unknown cause or be secondary to anoxia or endovascular stretch. Since collateral channels may be enhanced by vasodilation and since clinical experience indicates that temporarily anoxic neurones in border zones of ischemia are capable of revival, there is no reason to withhold stellate block from the patient with a recent nonhemorrhagic stroke. The fact that total cerebral blood flow is not increased by stellate block does not eliminate the possibility of improvement of local vascular irrigation. A safe but effective technic should be employed; the procedure is not to be relied upon to the exclusion of other therapeutic methods. Dramatic results are achieved in 3 to 5 per cent of patients, a moderate but definite response may be predicted in an additional 30 per cent and no effect is seen in 60 per cent or more (Naffziger and Adams).[33]

Cerebral Hemorrhage: A small but important group of patients are potential candidates for intracranial surgery after spontaneous cerebral hemorrhage. The clinical syndrome in these cases is: (1) initial verified brain hemorrhage with coma or stupor, (2) restoration of consciousness in the presence of lateralizing neurologic signs and (3) subsequent loss of alert behavior attended by other manifestations of increasing intracranial pressure. Lateral shift of the calcified pineal gland in plain x-ray films of the skull may be taken as adequate confirmatory diagnosis of intracerebral clot. Ventriculographic compression, in air-studies or displacement of the major cerebral arteries seen in angiograms, are better neuroradiologic localizing procedures. The results of surgery in such patients are good with respect to the episode; further complications of hypertensive cardiovascular disease usually appear subsequently. Operative intervention has nothing to offer the usual intraventricular flooding "hypertensive blow-out."

Cerebral Embolism: Since most instances of cerebral embolism originate from intravascular clots elsewhere, especially in the chambers or on the valves of the heart, it is apparent that the principal measure of prevention of initial or recurrent cerebral embolization is anticoagulant therapy.[39] The variability of blood coagulation in other types of brain stroke precludes routine use of such treatment except in the particular instances of suspected incipient thrombosis of the internal carotid or basilar arteries, extension of clotting from an arterial aneurysm treated by ligation of the main carotid vessel or migratory thrombophlebitis with intracranial involvement. The usually normal clotting time after cerebral infarction with or without thrombosis eliminates anticoagulant treatment as of any value in this condition and adds the possible danger of conversion of an anemic lesion into a hemorrhagic one.

Stellate block is the procedure of choice in initial therapy of the patient with sudden cerebral embolism, before anticoagulant drugs are administered. Persistent peripheral angiospasm has been proved to follow major cerebral arterial embolic occlusion. The effects of cerebral fat embolism may be counteracted by intravenous injection of calcium gluconate. During suspected air embolism the patient should be turned upon his left side immediately.

Cerebral Thrombosis, Infarction: Stellate block may be tried with possible benefit if angiospasm on the periphery of the lesion is significant. Polarographic study of the brain after experimental arterial occlusive lesions discloses a minimization of ischemia when pure oxygen is breathed.[23] The importance of maintenance of a normal systemic blood pressure should be emphasized. Recent clinical experience suggests that the addition of 5 to 7 per cent carbon dioxide to inhaled oxygen may be an aid to the development of collateral cerebral circulation.

Cortisone or hydrocortisone aid recovery from hemiplegia after cerebral infarction. Nicotinic acid (300 mg. three times daily) seems to be particularly beneficial following occlusion of the posterior inferior cerebellar artery.

Subarachnoid Hemorrhage: Intracranial

Aneurysm: Despite favorable reports of selected cases of ruptured intracranial aneurysm cured by intracranial clipping, the current mortality statistics in all patients with subarachnoid hemorrhage thus treated are cautionary. Proximal ligation of the cervical carotid artery is the procedure of choice in the control of aneurysms arising from the terminal intracranial carotid artery or its proximal branches, provided that preoperative occlusion demonstrates the ability of the brain to survive when inflow from one carotid has been sacrificed. Peripheral aneurysmal lesions may be dealt with directly as surgical judgment dictates. Since cervical carotid ligation reduces pressure in intracranial derivative vessels of small size almost as much as does clipping of the parent branch vessel,[3] decision as to the logical method of approach is difficult.

One knows that an aneurysm obliterated under direct vision is cured; one assumes that reduction of arterial pressure-head by cervical carotid ligation causes local thrombosis of the aneurysm. Long-term follow-up in reported series indicates that the latter event does occur; surgical mortality statistics favor cervical ligation rather than craniotomy. Two patients upon whom I operated recently had exactly similar aneurysms of the Sylvian middle cerebral artery revealed by angiography. One was treated by ligation of the carotid in the neck, the other by direct intracranial clipping. Both are doing well; the patient who underwent craniotomy has a spastic arm which he did not have prior to surgery. His aneurysm is definitely cured. The other patient is only assumed to be cured but is completely free of neurologic disability.

Arteriovenous Malformations: Surgical treatment is becoming more effective as operative technics are perfected and are assisted by planned hypotension or hypothermia. Direct approach to the lesion when possible is advocated by most neurosurgeons. The opinion has been expressed that carotid ligation is not only valueless but may be dangerous. I treated a patient with a large arteriovenous malformation of the middle cerebral artery and vein of Trolard by ligation of the common carotid artery. He had been operated upon previously (craniotomy) some years before, and tense brain was bulging through a large cranial defect. Diplopia was extreme and the patient was in coma. Intended excision of the lesion after preliminary arterial ligation was abandoned when cardiac arrest occurred. Nonetheless, the decompression became soft, double vision disappeared; the patient is now fully employed.

Several more such patients are apparently controlled after carotid ligation ipsilaterally with large arteriovenous anomalies demonstrated to be fed preferentially from one carotid artery. It is evident that the disease is not eradicated and it is realized that sizeable intracranial vascular malformations are often supplied by more than one major artery. However, it is important to note that a symptomatic response may be obtained by an indirect surgical approach when actual removal of the abnormal blood vessels might paralyze, otherwise cripple permanently or kill. Epilepsy, often symptomatic of these lesions, is not eliminated by surgery of any kind.

Intracranial Thrombophlebitis, Venous Thrombosis. The use of anticoagulant therapy is ideally suited to this type of cerebrovascular disease. Antibiotic drugs are also indicated in large dosage and for many months, if the inflammatory features of the disorder are thought to be bacterial in origin. By such treatment, patients suffering from cavernous sinus thrombosis, formerly inevitably fatal, are now being saved. Therapy must be prolonged and may require surgical assistance, such as drainage of subdural hygroma.

Hypertensive Brain Disease. In the management of hypertensive encephalopathy, lowering the elevated blood pressure usually proves adequate to clear the sensorium, stop seizures and release vasoconstriction. Careful intravenous "titration" with various ganglion blocking agents is advised. Magnesium sulfate is used in the control of eclamptic convulsions. Antiepileptic drugs should be employed in the combined presence of chronic hypertensive brain disease, an abnormal electroencephalogram and paroxysmal neurologic symptoms.

Cerebral Arteriosclerosis. Alvarez advises the old method of medicinal therapy, intravenous

and oral iodides, although he is not very enthusiastic. Since there is no real proof that food causes arteriosclerosis, decision concerning the advantage of a low fat diet has not been reached. The vasodilating effect of histamine administered cautiously often helps to overcome the effects of "little strokes." Sustained anticoagulant therapy has been suggested to prevent thrombosis when insufficiency of the basilar artery is suspected. Oral Metrazol is recommended for improvement in mood, orientation, industry and cooperation in patients with severe cerebral arteriosclerotic changes.[31]

General Management of the Patient. Contrary to previous misconception, physiologic saline solution given intravenously in the usual amount does not increase intracranial pressure. Intravenous glucose in water does result in rise of intracranial tension owing to blood hydration after the liver extracts sugar. With reference to intracranial pressure alone, the ideal parenteral solution is 2 to 5 per cent glucose in 0.42 per cent saline, this combination causes little disturbance of cerebrospinal fluid pressure and does not predispose to edema formation.[2] On the other hand, if hypernatremia develops, saline solutions are to be withheld until serum sodium values return to normal.

Much has properly been made of the beneficial effect of physiotherapy in helping to restore the hemiplegic patient to normal, to a working level or simply to a stage of self-care. Even simple home exercises may have almost as much effect as the more elaborate group programs in departments of physical medicine, although the latter are ideal. Learning on both the paretic and nonparetic sides of the body occurs chiefly in the first two months after brain injury.[35]

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ABSTRACTS

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HYPERTENSION

Hughes, W. M., Moyer, J. H. and Daeschner, W. C.: Parenteral Reserpine in Treatment of Hypertensive Emergencies. Arch. Int. Med. **95:** 563 (April), 1955.

Three groups of hypertensive patients were treated with parenteral reserpine on a short-term basis. The first group consisted of 14 patients with severe progressive hypertensive cardiovascular disease. In this group there were 10 patients with malignant hypertension and four patients with severe benign hypertensive cardiovascular disease. All the patients obtained a significant depression in blood pressure; in nine patients (64 per cent) the maximal depression in the supine position was in the normotensive range. Six of the 10 patients with malignant hypertension recovered from the malignant phase and are now well regulated on oral therapy. Uremia was present in four patients prior to the initiation of therapy, three of whom died as a result of uremia; one has severe uremia at the present time. The patients with severe benign hypertensive cardiovascular disease are living and are regulated on oral therapy.

The second group consisted of six patients with toxemia of pregnancy, four with severe pre-eclampsia and two with benign hypertensive vascular disease and associated severe pre-eclampsia. Normotensive levels were attained in all the patients. All the patients recovered. No fetal complications were observed.

The third group consisted of eight patients of pediatric age with acute glomerulonephritis. Seven of the eight patients obtained a significant reduction in blood pressure and six patients became normotensive. Six patients recovered, one progressed to a subacute stage of nephritis and one died as a result of congestive heart failure.

The blood pressure decreased slowly after a latent period of one to four hours after the parenteral administration of reserpine and attained a maximum depression two to five hours after administration. The blood pressure depression was manifested in the recumbent as well as the upright position. Excessive hypotension was rare.

The side-effects consisted of sedation, bradycardia, weakness, dreams and conjunctival injection. Muscle tremors developed after several days of therapy with large doses (5 to 10 mg.) administered at intervals of four to eight hours, and in one patient a Parkinson-like syndrome developed. This subsided completely after discontinuation of the drug.

Reserpine administered parenterally is an effective and safe agent for the treatment of hypertensive emergencies on a short-term basis.

BERNSTEIN

Rea, E. L. and Fazekas, J. F.: Effects of Parenterally Administered Reserpine. Arch. Int. Med. **95:** 538 (April), 1955.

Reserpine was administered parenterally in doses from 4 to 15 mg. to nine acutely disturbed subjects. Orthostatic hypotension was noted in two subjects and another died in shock. The electrocardiogram in the latter case revealed changes suggestive of myocardial toxicity, a finding that may account in part for the irreversible hypotension. Diarrhea has been observed following intravenous reserpine in dogs, but not in other animals. The loss of fluid and electrolytes attendant with diarrhea may have also contributed to the development of the shock syndrome.

The generalized flushing of the skin and respiratory distress noted in one of the subjects with orthostatic hypotension raises the possibility of an allergic reaction to the drug. The parenteral administration of reserpine in the management of acutely disturbed

alcoholics does not seem warranted in view of the lack of therapeutic response and occasional severe complications.

BERNSTEIN

Moyer, J. H., McConn, R. and Seibert, R. A.: The Effect of Blood Pressure Reduction with Arfonad on Renal Hemodynamics and the Excretion of Water and Electrolytes in Patients with Hypertension. Am. Heart J. **49:** 360 (March), 1955.

Arfonad was administered by continuous intravenous infusion to eight patients with hypertension. The concentration of the drug was 1 to 2 mg. per cc. in 5 per cent glucose in distilled water. The infusion rate varied between one and 10 mg. per mm. with an average of 4 mg. Observations were made on renal hemodynamics and on the excretion rates of water and electrolytes over a two-hour period of blood pressure reduction. As the blood pressure was reduced, glomerular filtration rate and water and sodium excretion were depressed and remained so during the entire period of blood pressure reduction.

RINZLER

PATHOLOGY

Billings, F. T., Jr. and Couch, O. A., Jr.: Pericardial Calcification and Histoplasmin Sensitivity. Ann. Int. Med. **42:** 654 (March), 1955.

Two histories are presented of patients with roentgenologically demonstrated calcification of the pericardium, with negative tuberculin and positive histoplasmin skin tests. It is, therefore, suggested that histoplasmosis may be another cause of calcification of the pericardium.

WENDKOS

PATHOLOGIC PHYSIOLOGY

Ungar, I., Gilbert, M., Siegel, A., Blain, J. M. and Bing, R. J.: Studies on Myocardial Metabolism. IV. Myocardial Metabolism in Diabetes. Am. J. Med. **18:** 385 (March), 1955.

Using the technic of coronary sinus catheterization, the authors investigated the changes occurring in the metabolism of the heart in patients with diabetes mellitus and in dogs with alloxan diabetes. The myocardial glucose usage of the diabetic heart was diminished relative to the normal heart. There was a marked decrease in usage of lactate by both the human and the dog heart. Myocardial usage of pyruvate was slightly diminished. Myocardial usage of ketones was slightly increased in diabetic patients and significantly elevated in diabetic dogs. The myocardial fatty acid extraction in diabetic patients was significantly increased, but normal in the diabetic animals. Insulin injection into diabetic dogs was without effect on myocardial glucose extraction. This suggests a relative increase in myocardial glucose utilization since the arterial glucose concentration declined. Insulin in several instances caused a negative pyruvate extraction by the heart. The hormone had no effect on the myocardial usage of lactate despite significant elevations in arterial lactate concentration. Arterial concentrations of fatty acids diminished following insulin without changes in myocardial usage and extraction of fatty acids. Insulin caused a diminution in arterial concentration of ketones and their myocardial usage. The consumption of amino acids by the diabetic heart remained unaffected by insulin despite a fall in arterial amino acid concentration. The results indicate that the diabetic heart is deficient in the metabolism of carbohydrates, proteins and fats.

HARRIS

Covino, B. G. and Charleson, D. A.: Ventricular Diastolic Threshold in Hypothermia. Am. J. Physiol. **181:** 257 (May), 1955.

At normal temperatures the ventricular threshold amperage rises after one to one and one-half hours to a value above 2.73 milliamperes. At temperatures of 24 C. (Thiopental) and 28 C. (Pentobarbital) the threshold was very variable. The range was from 0.5 to values over 2.73 milliamperes. At lower temperatures the results may be divided into two groups, one of which maintains a low threshold and the other does not during the hypothermia. Dogs, which have a ventricular threshold amperage that returns to high values during hypothermia, were observed to develop asystole at 15 to 18 C. Most of those which maintained a low threshold developed ventricular fibrillation at 19 to 26 C. Dogs were more apt to be in the low threshold group if the anesthetic was Pentobarbital. Also, these animals fibrillated at higher temperatures than those anesthetized with Thiopental.

OPPENHEIMER

Holliday, M. A.: Acute Metabolic Alkalosis: Its Effect on Potassium and Acid Excretion. J. Clin. Invest. **34:** 428 (March), 1955.

After three days on an electrolyte-deficient diet, followed by peritoneal dialysis resulting in hypochloremic alkalosis, rats received intraperitoneal injections of (1) a balanced fluid resembling extracellular fluid, (2) isotonic sodium bicarbonate, (3) hypertonic sodium bicarbonate, (4) sodium phosphate in addition to sodium bicarbonate and (5) sodium nitrate solution. Urine excretion and serum and muscle concentrations were studied.

The alkalotic animals excreted large amounts of potassium with a resulting reduction of muscle potassium and a gain in cell sodium. Furthermore, ingestion of sodium accentuated these changes. Potassium excretion was not significantly influenced by the pH or anion composition of the urine. Neither ammonia nor titratable acid excretion correlated with potassium excretion and the state of alkalosis did not diminish the ability of the kidney to excrete acid.

WAIFE

Hoffman, B. F., Suckling, E. E. and Brooks, C. McC.: Vulnerability of the Dog Ventricles and Effects of Defibrillation. Circulation Research **3:** 147 (March), 1955.

The authors were able, in experiments, to determine the boundaries of the vulnerable period within the cardiac cycle in which the dog ventricle was susceptible to fibrillation by means of a single test stimulus. The relative refractory period was found to be the only portion of the cardiac cycle during which fibrillation could be produced by this single test of stimulus method. This period of vulnerability usually coincided with the major dip of the strength interval curve. Defibrillation of the ventricle with countershock did not significantly alter the excitability or vulnerability.

SAGALL

Epstein, F. H. and Ferguson, T. B.: The Effect of the Formation of an Arteriovenous Fistula upon Blood Volume. J. Clin. Invest. **34:** 434 (March), 1955.

Using P^{32}-tagged red cells and the protein-binding dye, T-1824, the blood volume of seven dogs was measured before and after a large arteriovenous fistula was made surgically between the abdominal aorta and the inferior vena cava, halfway between the renal vessels and the bifurcation.

Up to a period of six weeks there was no change in total red cell volume but the plasma volume increased, resulting in an increase in total blood volume.

WAIFE

Prentice, T. C., Stahl, R. R., Dial, N. A. and Ponterio, F. V.: A Study of the Relationship between Radioactive Sodium Clearance and Directly Measured Blood Flow in the Biceps Muscle of the Dog. J. Clin. Invest. **34:** 545 (April), 1955.

Regional blood flow in muscle is often measured by the radioactive sodium clearance method. This study was planned to investigate the nature of the wide range of clearance values noted in normal and abnormal states.

Experiments on dog muscle revealed that, although a linear relationship was found to exist between total blood flow and radiosodium clearance from an intramuscular injection, the scatter of results was so great that the clearance rate could not be utilized as an accurate indicator of total blood flow. Anoxia was not found to be a contributing factor to the wide scatter of data.

The presence of effective shunts at the arteriolar level which by-pass a fraction of arterial blood around the capillary circulation could be a factor because radiosodium clearance is cleared presumably only by capillary flow. Clearance would then be correlated only with the fraction of total flow not shunted.

WAIFE

Alexander, J. K., West, J. R., Wood, J. A. and Richards, D. W.: Analysis of the Respiratory Response to Carbon Dioxide Inhalation in Varying Clinical States of Hypercapnia, Anoxia, and Acid-base Derangement. J. Clin. Invest. **34:** 511 (April), 1955.

Patients with cor pulmonale and chronic emphysema have a markedly reduced sensitivity to the stimulus of carbon dioxide-hydrogen ion as compared with normal subjects.

The diminished response to CO_2 could not be accounted for by increased blood buffering, presence or absence of congestive failure, chronic anoxemia or chronic acidosis. It does seem, however, that chronic hypercapnia, per se, results in a diminished sensitivity to carbon dioxide thus permitting an elevated carbon dioxide tension at rest. This in turn favors bicarbonate retention by the kidney. In time, a vicious cycle of increased carbon dioxide retention and diminishing respiratory sensitivity develops.

WAIFE

Relman, A. S., Roy, A. M. and Schwartz, W. B.: The Acidifying Effect of Rubidium in Normal and Potassium-Deficient Alkalotic Rats. J. Clin. Invest. **34:** 538 (April), 1955.

Rubidium is an alkali-metal element, which closely resembles potassium in physiologic, physical and chemical properties. In acute studies in rats, rubidium appears to be as effective as potassium in the ability to correct the alkalosis of potassium-deficiency. The acidifying effect is probably exerted through intracellular hydrogen exchange.

Chronic administration to normal or K-deficient alkalotic rats produced distinct extracellular acidosis, with bicarbonate values significantly below those of normal controls or those of animals given equivalent amounts of sodium or potassium chloride.

These studies suggest that intracellular cation replacement by rubidium is as effective as replacement by potassium in abolishing extracellular alkalosis. Furthermore, it appears that the alkalosis can be ameliorated without restoration of normal cellular cation composition, simply by administration of acid.

WAIFE

Torner-Soler, M., Balaguer-Vintró, I. and Gibert-Queraltó, J.: Elevated Right Ventricular Pressure. Am. Heart J. **49:** 538 (April), 1955.

A relationship was made between the electrocardiographic pattern and the level of systolic pressure of the right ventricle in 50 patients known to have right ventricular hypertension by right heart catheterization. Of the patients, one-half had congenital heart disease and the rest were mostly cases with mitral stenosis, a few having cor pulmonale. Four types of electrocardiograms were found: normal pattern, right bundle branch block, ventricular hypertrophy pattern and a mixed pattern of hyper-

trophy and blocking (right bundle branch block with a high R wave in lead V_1).

No normal patterns were found in patients with congenital heart disease with pressures over 30 mm. Hg. Above these values one found the ventricular hypertrophy pattern when the right ventricle suffers a systolic overcharge. The diastolic overcharge, an increase in pulmonary flow with or without right ventricular hypertension, produces the right bundle branch block pattern. The blocking patterns and hypertrophy coincide in patients with marked right ventricular hypertension and increased flow through the right ventricle.

In acquired heart disease, one usually finds normal or borderline tracings when there is no right ventricular hypertension or when this does not surpass 60 mm. Hg. Above this value, right ventricular hypertrophy tracings appear. The right bundle branch block is found at all pressure levels, generally below 80 mm. Hg, but its genesis remains confused.

In patients with congenital heart disease, there exists a relation between the degree of right ventricular hypertension and the height of the R wave in lead V_1. This relation is not very remarkable in the group with acquired heart disease, as in the latter the R wave is much less high for identical tension values. The greatest degree of alteration of activation time and height of the R wave in Lead V_1 in patients with congenital heart disease may be attributed to a greater ventricular hypertrophy due to a longer duration of the heart disease and the different conditions of the ventricular myocardium.

RINZLER

Gensini, G., Balchum, O. J. and Blount, S. G.: The Transmission of the Pulmonary Artery Pressure Across the Capillary Bed of the Lungs. Am. Heart J. **49:** 507 (April), 1955.

This study reports on the pulmonary artery wedged pressure and the pulmonary artery pressure contours in an attempt to determine whether undamped transmission of pulmonary artery pulses takes place and can be recorded. This was done in four patients. Pulmonary artery wedged pressure was analyzed in six patients.

The relationship of the wave forms and pressure levels of the pulmonary artery wedged pressure and pulmonary artery pressure have been compared in four patients, and the pulmonary artery wedged pressure analyzed in six patients. The resistance of the pulmonary vasculature and the magnitude of the pulmonary blood flow apparently had little effect upon the transmission of the pulmonary artery pressure within the limits of this study. In pulmonary valvular stenosis the pulmonary artery wedged pressure is greater than the pulmonary artery pressure. This is due to the greater degree of stenosis that exists when the cardiac catheter is present in an already stenotic pulmonary valvular orifice. Therefore, it would appear that the pulmonary artery wedged pressure is a more accurate estimation of the pressure actually existing in the pulmonary artery in the case of pulmonic stenosis. The effect of the pulmonary valve stenosis, on the time of onset of the pressure pulses in the pulmonary artery and pulmonary artery wedged pressure, has been observed and compared to that of patients with normal pulmonary valves.

RINZLER

Covino, B. G. and Williams, L.: Excitability Cycle of the Ventricle in Hypothermia. Am. J. Physiol. **181:** 362 (May), 1955.

The current of injury which appears in the electrocardiogram of hypothermic dogs is observed at the time when the threshold is very low during the minor dip in the excitability cycle. This injury current results from respiratory acidosis and low blood pH. It is concluded that this explains the low threshold. There is correlation between current of injury during a bout of hypothermia and ventricular fibrillation. Latency is longer for stimuli which are applied early in the cycle. Latency is reciprocally related to temperature of the heart.

OPPENHEIMER

Imig, C. J., Roberson, W. J., Gault, M. and Hines, H. M.: Blood Flow in the Hind Legs of Dogs after Exposure to Cold. Am. J. Physiol. **181:** 395 (May), 1955.

Volume flow increases in the hind foot or hind leg when rewarming follows exposure to temperatures of 0 C. or below. On the other hand, if the parts were cooled to 15 C. for 30 minutes the volume flow was not significantly changed in the recovery period. However, if cooling at 12 C. persisted for three and one-half hours, then warming was observed to increase flow.

OPPENHEIMER

Blake, W. D. and Davidson, D. G.: Some Effects of Repeated Injections of Epinephrine and of an Adrenergic Blocking Agent on the Daily Excretion of Water and Electrolytes in the Dog. Am. J. Physiol. **181:** 423 (May), 1955.

Both epinephrine-in-oil and Hydergine first increase sodium excretion but later produce a somewhat larger decrease. Epinephrine decreases potassium excretion but not that of chloride. Hydergine increases both potassium and chloride excretion. Adrenalectomy does not prevent the late phase of Hydergine sodium retention.

OPPENHEIMER

Kleinfeld, M., Greene, H., Stein, E. and Magin, J.: Effect of the Cadmium Ion on the Electrical and Mechanical Activity of the Frog Heart. Am. J. Physiol. **181:** 35 (April), 1955.

Cadmium chloride shortens action potential dura-

tion and decreases membrane action potential voltage. P-R interval is increased early and there are later changes in QRS and T. The atrium dilated first and the ventricle did so later. Cardiac output was decreased. Cardiac arrest took place in diastole. Cadmium actions were not changed by cysteine, although, if cysteine was given first, there was a slight delay in cadmium effects. Cadmium may have a metabolic effect and also one on the membrane.

OPPENHEIMER

PHARMACOLOGY

Moyer, J. H. and Handley, C. A.: Renal and Cardiovascular Hemodynamic Response to Ganglionic Blockade with Pendiomide and a Comparison with Hexamethonium and Arfonad. J. Pharmacol. & Exper. Therap. **113:** 383 (April), 1955.

There is a continuing search for agents which will lower blood pressure. Pendiomide is a new hypotensive agent which blocks transmission of nerve impulses across the sympathetic ganglion. Renal and cardiovascular responses of this drug were studied and compared to those of hexamethonium and Arfonad.

The effects of these drugs were studied on eight anesthetized dogs. Creatinine was used to measure glomerular filtration rate (GFR), PAH for renal plasma flow (RPF), and glucose for maximum reabsorptive capacity (TmG.). Blood pressure (MBP) was measured by a clamped mercury manometer. Cardiac outputs were estimated in five anesthetized dogs, using the pulse contour method of Hamilton and Remington.

Six to 12 mg. of Pendiomide, intravenously, reduced the blood pressure (MBP) significantly from 141 to 115 mm. Hg. ($p < 0.01$) but did not change glomerular filtration rate (GFR) or renal plasma flow (RPF). Renal vascular resistance decreased and renal blood flow did not change. One hour later the MBP had returned to normal without any change in GFR or RPF Glucose for maximum reabsorptive capacity (TmG) was not altered. Continuous infusion of the drug maintained the reduction in blood pressure longer than a single injection of the drug, but it did not alter renal hemodynamic responses. Hexamethonium produced similar renal hemodynamic responses but a greater drop in blood pressure. Arfonad produced an even greater decrease in blood pressure and a decrease in glomerular filtration rate, which was probably caused by this greater drop in blood pressure. Increasing the blood pressure back to control levels with norepinephrine did not depress renal plasma flow or glomerular filtration rate. However, elevation of blood pressure to hypertensive levels depressed renal blood flow and glomerular filtration rate. Water and sodium excretion followed a similar pattern of response.

Pendiomide caused an initial increase in cardiac output followed by a moderate reduction. In one hour the cardiac output returned to normal.

Intravenous pendiomide in doses of 6 to 12 mg. per Kg. in dogs decreased blood pressure, but renal blood flow and function was maintained. These results are similar to those obtained with hexamethonium, although this drug and Arfonad depressed the blood pressure to a greater extent. Norepinephrine will increase the blood pressure and maintain or return renal function to normal level.

WECHSLER

Winsor, T. and Scott, C. C.: Further Observations of Cardiovascular Effects of Pentaerythritol Tetranitrate in Animals and Man. Am. Heart J. **49:** 414 (March), 1955.

The sublingual administration of pentaerythritol was studied to determine if it was absorbed by this route and to determine the effect on the cardiovascular system of man and dogs. In dogs the coronary blood flow increased significantly, with a slight decrease in blood pressure without significant alteration of pulse rate. These changes indicate the presence of coronary vasodilation. In man the pulse rate increased slightly, without significant change in blood pressure. The IJ wave of the ballistocardiogram increased slightly. There was only minimal increase in skin temperatures, height of pulsations, and relative blood flow of the digits. An increase of slightly more than two minutes in exercise tolerance was observed. The agent was absorbed as a dust by the pulmonary epithelium. Orally, pentaerythritol was more effective in large doses (69 mg. per day) than in small doses (34.6 mg. per day). It was likewise more effective for the prophylaxis of angina pectoris in small oral doses than was 10 mg. of triethanolamine trinitrate per day.

RINZLER

Rubini, M. E., Kleeman, C. R. and Lamdin, E.: Studies on Alcohol Diuresis. I. The Effect of Ethyl Alcohol Ingestion on Water, Electrolyte and Acid-Base Metabolism. J. Clin. Invest. **34:** 439 (March), 1955.

The diuresis which follows alcohol ingestion is usually ascribed to suppression of release of the antidiuretic hormone. Further metabolic aspects were studied on three young male subjects.

After the ingestion of 120 cc. of 100 proof bourbon, blood alcohol levels rose and reached their peak at about 90 minutes. There was an increased urine flow with a decrease in excretion of solutes; that is, an increase in free water clearance. The decrease in solute excretion is ascribed to redistribution of blood volume.

An extracellular acidosis also developed with a rise in titratable acid and ammonia and a fall in bicarbonate. These findings are consistent with the hypothesis that alcohol inhibits the supraoptico-hypophyseal system.

WAIFE

Kleeman, C. R., Rubini, M. E., Lamdin, E. and Epstein, F. H.: Studies on Alcohol Diuresis. II. The Evaluation of Ethyl Alcohol as an Inhibitor of the Neuro-Hypophysis. J. Clin. Invest. **34:** 448 (March), 1955.

In this companion study it was found that after the administration of hypertonic sodium chloride solutions (or venous congestion of the extremities), the characteristic fall in urine flow could be minimized or prevented by alcohol. Furthermore, the antidiuresis of dehydration, or acetylcholine or nicotine administration, can also be prevented by alcohol. In addition, alcohol has no effect on urine flow when given at the height of water diuresis.

From these and other studies the authors conclude that alcohol acts by inhibiting the release of antidiuretic hormone.

WAIFE

Hoffman, B. F., Siebens, A. A., Cranefield, P. F. and McBrooks, C.: The Effect of Epinephrine and Norepinephrine on Ventricular Vulnerability. Circulation Research **3:** 140 (March), 1955.

Studies in dogs with electrical stimuli through indwelling cardiac electrode showed that *l*-epinephrine and *l*-norepinephrine had similar qualitative and quantitative effects in increasing the vulnerability of the ventricular musculature to fibrillation. Both drugs caused a brief enhancement and then a long-lasting and less marked depression of vulnerability. There was no difference between the drugs, either in the frequency with which fibrillation followed their use or in the ease of defibrillation by means of countershock. The effects of vulnerability were related to the dose employed and coincided with changes of similar direction in the level of the resting excitability of the ventricular muscle. The changes in excitability and fibrillation thresholds, however, do not appear to be causally related, but probably are reflections of independent actions of the drugs.

Since both drugs have similar effects, it would appear that the clinically reported greater safety of norepinephrine arises from the fact that it is usually given in high dilution rather than from any specific pharmacologic attribute, differentiating it from epinephrine in this regard.

SAGALL

Stone, H. W., MacKrell, T. N. and Wechsler, R. L.: The Effect on Cerebral Circulation and Metabolism in Man of Acute Reduction in Blood Pressure by Means of Intravenous Hexamethonium Bromide and Head-Up Tilt. Anesthesiology **16:** 168 (March), 1955.

This study was aimed at determining whether or not the intentional reduction of blood pressure employed clinically in surgical operations by hexamethonium impaired the average cerebral circulation and metabolism. Ten random hospitalized patients were selected for investigation. Systemic hypotension was produced by the intravenous injection of hexamethonium bromide and a 15 degree head-up tilt. A comparison was made between the arterial and internal jugular blood gases, cerebral blood flow, oxygen consumption and vascular resistance before and after the procedure. The cerebral blood flow and oxygen consumption were not found to be significantly altered by an average reduction of 44 per cent in the mean arterial blood pressure. The cerebral circulation in the presence of the induced hypotension was maintained by a significant and adequate reduction in cerebrovascular resistance. Decreases in the arterial and internal jugular oxygen content were found after the induction of hypotension. The fact that this occurred without an increase in cerebral metabolism probably reflects an increase in the total blood volume.

SAGALL

Williams, T. F., Hollander, W., Jr., Strauss, M. B., Rossmeisl, E. C. and McLean, R.: Mechanism of Increased Renal Sodium Excretion following Mannitol Infusion in Man. J. Clin. Invest. **34:** 595 (April), 1955.

Mannitol, when administered intravenously, promotes the urinary excretion of sodium, chloride and water. In this study, isotonic or slightly hypotonic Mannitol solution was given to normal, sitting, water-loaded subjects. The expected saluresis resulted. Comparable expansion of the extracellular fluid volume by hypotonic sodium chloride-sodium bicarbonate solution failed to induce a similar increased excretion of the electrolytes; it was concluded that the Mannitol effect was not produced by cellular dehydration, or expanded extracellular fluid volume, but rather by a direct effect in the renal tubule.

WAIFE

Mitchell, E. H.: Chlorpromazine in the Treatment of Acute Alcoholism. Am. J. M. Sc. **229:** 363 (April), 1955.

This study was made on 306 patients, representing 400 admissions for treatment of acute alcoholism. One half of the cases received Chlorpromazine as the primary therapeutic agent and one half were sedated with barbiturates and Mephenasin. The former group were given 50 mg. intramuscularly or by vein; following this they received 50 to 100 mg. orally every four hours. The latter group received intravenously 250 mg. of Secobarbital and Butobarbital and 100 mg. of Mephenasin every 3 hours until bedtime. In those receiving Chlorpromazine, mild postural hypotension developed in 43 instances and severe hypotension in seven instances. Lowering of the dose of the drug controlled the hypotensive effects. Tachycardia, noted in 22 cases, disappeared when the drug was stopped. There was one death in the Chlorpromazine group in a poor-risk cardiac patient with hepatic cirrhosis. The results obtained

in the Chlorpromazine group were encouraging in 85 per cent of the 200 cases studied. There was an effective sedative effect; nursing care was simplified and the patients were more amenable to treatment; food was retained earlier; discharge from the hospital was effected on an average of 24 hours earlier than the barbital group.

SHUMAN

Covino, B. G., Wright, R. and Charleson, D. A.: Effectiveness of Several Antifibrillary Drugs in the Hypothermic Dog. Am. J. Physiol. **181:** 54 (April), 1955.

Dogs were subjected to immersion hypothermia. Fifty per cent or more of these under Nembutal anesthesia die in ventricular fibrillation. Dilantin requires doses large enough to depress the sinoatrial node in order to control ventricular fibrillations. The Dilantin depression added to that of cold produces asystole at a temperature comparable to that at which fibrillation was observed before Dilantin was used. Procaine amide caused ventricular fibrillation in hypothermic dogs at doses of 5 to 25 mg. per kilogram provided Dacorene is given in divided doses up to 8 to 15 mg. per kilogram, it will protect most dogs from hypothermic ventricular fibrillation. Single large doses of Dacorene lower ventricular threshold and often cause fibrillation. In the case of small doses, repeated frequently, the threshold is elevated briefly with each administration.

OPPENHEIMER

Farah, A. and Koda, F.: The Action of Mercurial Diuretics on Urinary Sodium Concentrations and Urine Volume. J. Pharmacol. & Exp. Therap. **113:** 256 (March), 1955.

It has been postulated that mercurial diuretics increase urinary excretion of electrolytes and water by acting on two separate reabsorption mechanisms; one mainly concerned with urinary sodium concentration, the other controlling urine volume. Roeser and Burch demonstrated that mercurials increased sodium excretion prior to the urine volume changes.

In anesthetized and unanesthetized dogs, creatinine and paraaminohippurate clearances as well as sodium, potassium and chloride in plasma and urine were determined. In 5 of 14 studies 0.5 to 1.5 mg. of Mersalyl, intravenously, increased urine to sodium concentration with no increase in urine flow and no change in glomerular filtration rate. The dosage of the mercurial necessary to produce this change was critical. Large doses of Mersalyl increased both urine volume and sodium concentration. There were no consistent changes in potassium excretion. The effects of small doses of Mersalyl on urinary sodium concentration could be reversed by 5 mg. per kilogram of 2,3 dimercaptopropanol (BAL), intravenously. These studies indicated that the mercurial affected two independent processes in the kidney.

Large doses of Mersalyl with cysteine were given intravenously and, at the height of the diureses graded small doses of 2,3 dimercaptopropanol (BAL) were also given intravenously. In four of eight experiments, this procedure reversed the mercurial induced urinary volume change, without decreasing the sodium concentration changes. Intravenous 2,3-dimercaptopropanol alone did not reduce urine flow, glomerular filtration and plasma flow. Urinary sodium concentration was not increased. These results suggest that the reversal of the mercurial induced urine volume changes is due to a partial reversal of the mercurial diuresis.

The findings support the theory of separate concentration and volume controlling mechanisms in the mammalian kidney.

WECHSLER

Massumi, R. A. and Evans, J. M.: Studies on the Continuous Use of a Carbonic Anhydrase Inhibitor (Diamox) in Ambulatory Patients. Am. Heart J. **49:** 626 (April), 1955.

Diamox was administered orally to 30 ambulatory patients with edema for periods of one and one-fourth to eight and one-half months. The results were good to excellent with maintenance of satisfactory cardiac compensation in 19 (63.6 per cent) of the 30 subjects. The response was usually less satisfactory in patients with long-standing and recurrent right-sided heart failure and fixed hepatomegaly. In nine patients side effects were severe enough to require discontinuance in two of the nine patients. It is felt that Diamox is a safe and effective oral diuretic for use in ambulatory patients. The drug may be useful in combating edema of the nephrotic syndrome and may have a place in managing edema due to venous insufficiency.

RINZLER

PHYSICAL SIGNS

Spitzbarth, H.: Chemical Studies Concerning the Genesis of Functional Systolic Murmurs of the Pulmonic Valve. Arch. f. Kreislaufforsch. **22:** 1 (March), 1955.

Among 112 persons, 12 to 52 years old, the authors found a functional systolic murmur in 68 per cent, with prevalence in individuals under 35 years. The hemodynamic conditions leading to such a murmur were studied by the methods of Broemser-Ranke and Blumberger.

A functional systolic murmur occurs when the peripheral vascular resistance is diminished and cardiac output is high. Under such circumstances, arterial pressure curves show a steep ascent, a short plateau, and an incisure low in the descending limb. Alterations of the hemodynamics, affected by various drugs, revealed that appearance and disappearance of a functional murmur was invariably related to the presence or absence of these changes in hemodynamics and to the characteristic pulse pressure contour. Development of a murmur is explained by

ly formation in the large vessels engendered by re rapid blood flow in the first part of ventricular ction against reduced peripheral resistance. The re frequent occurrence of a functional systolic rmur in childhood and its location is explained the topography of the right ventricle and the ference of right and left ventricular dynamics in ildren and adults. A functional systolic murmur a physiologic and expected finding in children, ung persons and following exercise. The concept a "tachycardia murmur" is rejected by the thors.

PICK

Luisada, A. A., Haring, O. M. and Zill, A. B.: Apical Diastolic Murmurs Simulating Mitral Stenosis. II. Graphic Differentiation. Ann. Int. Med. **42:** 644 (March), 1955.

A study of the graphic characteristics of apical murmurs simulating those of mitral stenosis was made in 34 cases. The "functional" nature of the murmur was proved by autopsy in 11 cases, by disappearance following surgery (not on the mitral valve) in two cases, and by appearance of the murmur during observation and subsequent disappearance following improvement in 21 cases. Certain positive data were found helpful in recognizing the nature of the murmur; the murmur is frequently loud and occurs later in diastole; it is often recorded over a large area of the chest; there frequently is a third sound. Certain negative data were also found helpful: there is no opening snap; the main vibration of the first sound has a normal relationship with the QRS complex. Graphic data permit one to recognize the "functional" nature of the murmur in a great majority of the cases. The murmur in these cases seems to depend on a *relative stenosis* of the mitral valve (disproportion between normal mitral ostium and large left ventricle, creating eddies within the ventricle). The large area of recording can be explained by the large area of contact of the left ventricle (coronary and hypertensive cases), or of both ventricles (acute carditis), with the precordium. In the latter cases, *relative stenosis of both the mitral and tricuspid valves* is likely. It should be noted that some of the graphic characteristics, and in particular the amplitude of the murmur, can be recognized best on a "stethoscopic" tracing which does not distort the picture by increasing the high pitched vibrations.

WENDKOS

PHYSIOLOGY

Ersten, B. and Li, T. H.: Hemodynamic Changes during Thiopental Anesthesia in Humans: Cardiac Output, Stroke Volume, Total Peripheral Resistance, and Intrathoracic Blood Volume. J. Clin. Invest. **34:** 500 (March), 1955.

Hemodynamic studies were performed on 14 subjects undergoing anesthesia by Thiopental, given by intravenous drip, after morphine-scopalamine preanesthesia.

The cardiac output which was unchanged during hypnosis fell about 25 per cent during deep anesthesia. Changes in stroke volume and intrathoracic blood volume (as measured by Evans blue dye and catheterization) paralleled the cardiac output. These effects are probably the result of the redistribution and pooling of blood, resulting in a diminished venous return.

WAIFE

Poppi, A., Barbieri, L. L., Martinelli, M. and Marini, M.: The Effect of Intravenous Administration of Cocarboxylase, of Riboflavin and of Alloxazine Mononucleotide (AMN) on the Oxygen Debt in Heart Patients. Cardiologia **26:** 173 (Fasc. 3), 1955.

In 20 cardiac patients, the oxygen debt was determined before and after intravenous administration of 50 mg. of cocarboxylase, riboflavin or alloxazin mononucleotide. Each of the three substances caused a sharp reduction of the oxygen debt by 55 to 72 per cent. Two hypotheses, to explain these observations, are advanced and discussed. The first, enhancement of utilization of oxygen in the tissues is in accordance with present knowledge and complies better with the facts observed than the other, which invokes a cardiotonic effect of the three agents used.

PICK

Zissler, J.: The Effects of some Cardiac Glycosides on Hemodynamics in Man. Arch. f. Kreislaufforsch. **22:** 97 (March), 1955.

A comparative clinical study is presented of various digitalis preparations evaluated on the basis of their effects on the circulating blood volume and venous pressure, in terms of Wollheim's concepts of "plus and minus decompensation."

In acute experiments on normal persons, intravenous application of strophanthin, Digipurate and Digitoxin causes distinct reduction of the active blood volume. Strophanthin exerts a rapid but only transitory action, while Digitoxin acts slowly and permanently. Cedilanid lowers the blood volume in rare cases. These findings in normal subjects illustrate the extracardiac effects of the various glycosides. The exact mechanism of their action under such circumstances is disputed. It could represent a direct effect upon peripheral vessels, as well as an indirect reflex action upon the heart of the Bezold-Jarisch type.

In long term clinical therapeutic experiments, strophanthin, Cedilanid, Digipurate and Digitoxin, applied in comparable dosage, act qualitatively in a similar way. There are differences in the rapidity and intensity of the action of the various preparations, which can be explained on the basis of differences in their chemical structure and tendency to

cumulation. In "plus decompensation" with increased blood volume (the absolute indication to digitalis therapy according to Wollheim), the preparations with maximal cumulation (Digipurate and Digitoxin) are most efficient. Cedilanid, having primarily cardiac and little extracardiac effects (as revealed in the acute experiments on normals), is indicated in "minus decompensation," that is, in cardiac failure attributable to impaired venous return and in impending or developed peripheral circulatory failure.

PICK

Maguire, R. X. and Merendino, K. A.: Effect of Age on Mechanism of Death and Ability to Tolerate Acute Hypothermia in Dog. Arch. Surg. **70:** 367 (March), 1955.

By means of a cooling blanket, the effect of hypothermia was studied in a group of 30 dogs. The cooling was continued until death occurred. The mechanism of death in adult dogs was found to be ventricular fibrillation, while in juvenile dogs it was cardiac arrest. Furthermore, fatal cardiac alterations in rhythm were noted at significantly lower temperature in immature animals.

It was the opinion of the authors that hypothermia of itself may create serious problems. This must be dealt with properly, or the risks imposed are too great for the short additional time gained by the procedure for the intracardiac operation.

ABRAMSON

Berglund, E., Sarnoff, S. J. and Isaacs, J. P.: Ventricular Function. Role of the Pericardium in Regulation of Cardiovascular Hemodynamics. Circulation Research **3:** 133 (March), 1955.

The authors studied the influence of the pericardium on cardiovascular hemodynamics in dogs, when the circulation was subjected to abnormal stresses. The data showed that when the left ventricle was stressed, as by an increased resistance in the aorta, that chamber would dilate and occupy a disproportionately larger part of the pericardial space. The intact pericardium was found to limit the diastolic expansion of the right ventricle and, therefore, the work of that chamber. This prevents the increased pulmonary capillary and left atrial pressures which would otherwise develop in such situations. The pericardium thus acts as a restraining influence on the edemogenic tendencies due to increased pulmonary capillary pressure which would develop in hypertensive heart disease and similar conditions, where the left ventricle is subjected to increased work and dilatation.

The pericardium also was found to protect against tricuspid or mitral valve regurgitation at high ventricular filling pressures. This may account for the observed descending limb of the classically conceived Starling curve.

SAGALL

Dawe, A. R., and Morrison, P. R.: Characteristics of the Hibernating Heart. Am. Heart J. **49:** 367 (March), 1955.

The hearts of the hibernating hedgehog, Arctic ground squirrel and Franklin ground squirrel have been studied electrocardiographically. Heart rates were described during the periods when animals are going into, during and coming out of hibernation. Heart rate in these periods can be shown with reference to time and body temperature. In reference to time, they are cyclic in periods of several days, to temperature, the function is different going into than coming out of hibernation. Going into hibernation, the heart shows a hyperirritability beginning at a body temperature of about 20 C. which precludes heart standstill as it would occur in most other mammals on cooling. In deep hibernation, the heart rate is greatly slowed to values as low as 2.2 beats per minute but stabilizes at body temperature somewhat above ambient temperatures, on an average 2.1 C. above ambient temperatures in the three species. The heart rate may show unusual patterns such as pairing of beats or beats in bursts. Coming out of hibernation the rise in heart rate precedes the rise in body temperature.

Since the heart rates have descended to very low values, the components of the electrocardiograms in deep hibernation in all three species have been greatly stretched or extended by comparison to the components of nonhibernating lightly anesthetized animals of the same species. The stretch or extension of these components is of the following order of magnitude: (1) The T-P interval is lengthened far and beyond all other components, that is, the automaticity of the S-A node is most particularly slowed in hibernation. (2) The P-R is the next most lengthened interval, that is, the conduction time is the next most increased component. (3) The QRS interval, P interval and Q-T interval are in decreasing order. The RS-T interval shows the least amount of extension or stretch due to hibernation. If this is strictly representative of a temperature effect, it may be an indication that the RS-T reflects the time of a cellular electrolytic reaction. It is reasonable that the Q-T stretch be intermediate in value between the QRS and RS-T, since it is largely composed of these two intervals.

RINZLER

Fishman, A. P., Himmelstein, A., Fritts, H. W. Jr., and Cournand, A.: Blood Flow through each Lung in Man during Unilateral Hypoxia. J. Clin. Invest. **34:** 637 (April), 1955.

By a special procedure involving bronchospirometry, cardiac catheterization and arterial cannulation, it was possible to study the blood flow through each lung. During unilateral breathing of hypoxic gas mixtures, no alteration in total minute blood flow, or in distribution of blood to each lung was found, although the mixture was capable of

creasing pulmonary arterial pressure, when applied both lungs.

It would appear that the hypoxic stimulus does not act directly on the lung nor on postarteriolar segments of the pulmonary vascular system to increase the resistance to blood flow. Mechanisms, other than reflex vasoconstriction of the pulmonary bed, must be involved in arterial hypoxemia and a shift of blood, to the lungs from systemic vasoconstriction after hypoxia, may be a factor.

WAIFE

Andres, R., Zierler, K. L., Anderson, H. M., Stainsby, W. N., Cader, G., Ghrayyib, A. S. and Lillienthal, J. L., Jr.: Measurement of Blood Flow and Volume in the Forearm of Man; with Notes on the Theory of Indicator-Dilution and on Production of Turbulence Hemolysis and Vasodilatation by Intra-Vascular Injection. J. Clin. Invest. **33:** 482 (April), 1954.

The authors measured blood flow through the forearm of 27 subjects using the dye dilution principle. This was accomplished through a continuous injection of Evans blue dye, T-1824, into the brachial artery by means of a jet injector. Venous blood samples were collected by means of a catheter directed downward in the blood stream. In the majority of subjects, adequate mixing of dye and blood was achieved to produce uniformity of dye distribution.

By the above method, resting blood flow varied from 2.7 to 7 ml. per minute per 100 ml. of forearm. with a mean of 4.4. These figures were about 50 per cent greater than those measured by plethysmography. It was conceded that the use of the dye-dilution principle in the determination of local circulation was more cumbersome than plethysmography. However, the method was well-suited for study of local metabolism since it permitted continuous registration of blood flow with excellent reproducibility.

ABRAMSON

Ruef, J., Bock, K. D. and Hensel, H.: The Effect of Smoking upon Blood Supply to Muscles. Ztschr. f. Kreislaufforsch. **44:** 272 (April), 1955.

The authors report calorimetric studies in 27 normal persons before and following smoking of a cigarette with 1.44 per cent nicotine content. The temperature was recorded in the muscles of the thigh or forearm, simultaneously with the skin temperature of the hand or foot.

In all experiments, the skin temperature fell upon smoking and the spontaneous rhythmicity of cutaneous vasomotion was reduced or disappeared. Blood supply to the muscles, on the other hand, as measured by changes in their temperature, increased in the majority of the experiments by 40 per cent on the average, with the maximum of increase occurring 10 to 13 minutes following smoking. Effects of hyperventilation could be ruled out. There was no significant difference in the results of experiments performed on habitual smokers and non-smokers. A slightly lower effect in the latter group could be ascribed to less absorption of nicotine due to non-inhaling. The observed effects of smoking are ascribed by the authors to increased release of epinephrine by the adrenal glands.

PICK

Vidt, D. G., Hanusek, G., Schieve, J. F., Hull, H. B. and Sapirstein, L. A.: Spontaneous Variability of Cardiac Output in the Dog. Am. J. Physiol. **181:** 337 (May), 1955.

Rose Bengal was used to determine cardiac output by the dye dilution technic. Spontaneous and entirely unexpected variations in output were observed during serial determinations. These variations were found in trained, unanesthetized dogs and those under pentobarbital anesthesia. Direct Fick determinations using para-aminohippurate (PAH) confirmed the findings recorded by the dye technic.

OPPENHEIMER

Smith, D. L., Maaske, C. A. and Julian, F.: Respiratory Response to Partial Occlusion of the Main Pulmonary Artery in the Dog. Am. J. Physiol. **181:** 341 (May), 1955.

The authors have developed a method for repeatedly constricting the main pulmonary artery in the unanesthetized dog. As the pulmonary artery is constricted, there is a fall in systemic blood pressure. Central venous pressure rises. At the same time there is a period of hyperpnea and tachypnea. The increased respiration depends on the systemic hypotension and reduced pulmonary blood flow. It is independent of the elevated central venous pressure.

OPPENHEIMER

Clonninger, G. L. and Green, H. D.: Pathways Taken by the Sympathetic Vasomotor Nerves From the Sympathetic Chain to the Vasculature of the Hind Leg Muscles of the Dog. Am. J. Physiol. **181:** 258 (May), 1955.

Stimulation of the lumbar sympathetic chain produced both dilator and constrictor responses when blood flow was observed in the femoral artery supplying skeletal muscle of thigh and upper calf. Eighty-nine and one-tenth per cent of the response was mediated via sciatic nerve and 8.7 per cent in nerves around the femoral artery. The femoral nerve carried 2.2 per cent of the fibers.

OPPENHEIMER

Zankel, H. T., Shipley, R. A. and Clark, R. E.: Effect of Posture and Local Pressure on Venous Circulation Time of the Leg. Arch. Phys. Med. & Rehab. **36:** 226 (April), 1955.

Using radioiodine as a tracer material, the authors studied venous circulation time from the foot to the

groin under various circumstances. A dose of 5 μc. of I^{131} was injected into the dorsal vein of the foot while a scintillation counter, placed over the groin at the saphenofemoral junction, was used to determine the time of arrival of the material at this site.

The application of a constricting pressure of 10 to 20 mm. Hg to the calf, using a blood pressure cuff, reduced the circulation time, while a higher pressure reversed this effect. Elevation of the leg with the subject recumbent, produced a marked decrease in time, except in patients with arteriosclerosis obliterans in whom the figures were increased. Flexion of the knee and assumption of a sitting position resulted in no consistent effect. In the upright position the time was prolonged.

ABRAMSON

Shepherd, J. T., Bowers, D. and Wood, E. H.: Measurement of Cardiac Output in Man by Injection of Dye at a Constant Rate into the Right Ventricle or Pulmonary Artery. J. Appl. Physiol. **7:** 629 (May), 1955.

The major problem in applying the dye dilution principle to the measurement of cardiac output is the rapid recirculation of the dye. Therefore, the equilibrium concentration at the sampling site may not be clearly defined. In order to circumvent this difficulty, the right ventricle or pulmonary trunk was chosen as the injection site. This maneuver resulted in an increased duration and better definition of the equilibrium concentration.

These studies were accomplished on healthy physicians and patients with heart disease. Dye dilution curves were recorded at the right radial artery and both ears following the sudden single injection of Evans blue dye (T-1824) through a cardiac catheter placed in the right ventricle or pulmonary artery. In four studies the sudden single injection was made after the constant rate injection. Cardiac output was also measured by the direct Fick principle.

The dilution curves recorded simultaneously by a cuvette oximeter at the radial artery and the ears were similar in contour. Studies were accomplished which showed that dye concentration remained at equilibrium a mean of 2.7 seconds before recirculation occurred. Comparison of cardiac output values determined by the direct Fick, constant rate dye injection and sudden single dye injection methods failed to reveal any systematic differences. The standard deviation of the differences between the paired Fick and constant rate dye injection values was 10 per cent, between Fick and sudden single dye injection values was 16 per cent and between sudden single and constant rate injection values was 16 per cent. The average time interval between these paired determinations was five, six and nine minutes respectively.

The constant rate injection version of the indicator or dye dilution technic is a reliable method for the measurement of cardiac output in man when the injection site is the pulmonary artery or right ventricle.

WECHSLER

Reed, E. A. and Scott, J. C.: Factors Influencing the Carotid Sinus Cardioinhibitory Reflex. Am. J. Physiol. **181:** 21 (April), 1955.

If one vagus is cut, the cardioinhibitory response to bilateral manual compression of the carotid sinus is decreased acutely. In the chronic state the reverse is true. Dogs, anesthetized with Pentothal to a depth so that oxygen saturation is reduced, have a much less responsive cardioinhibitory reflex after oxygen is administered. Changes in arterial pH are not a factor in these responses.

OPPENHEIMER

Watson, L. S., Gullixson, K. S., Rennie, D. W. and Youmans, W. B.: Effect of Hemorrhage on Renal Handling of Sodium in Normal and Adrenalectomized Dogs. Am. J. Physiol. **181:** 140 (April), 1955.

Hemorrhage in normal dogs decreases the sodium load and there is a larger decrease in sodium excretion. After reinfusion, the sodium load rises as glomerular filtration rate increases. Sodium excretion continues to decrease or remains at a low level. Reinfusion in adrenalectomized animals did not restore sodium load. Glucose solution contributes to failure in these adrenalectomized animals since both plasma sodium and potassium are reduced. Normal dogs sometimes excrete very small amounts of sodium even though the load is normal. This never happens in adrenalectomized animals which always excrete sodium, if the load is normal. However, if the load is reduced they may then fail to excrete sodium. There is no data to support the possibility that adrenalectomized animals can increase tubular reabsorption if there is a normal sodium load.

OPPENHEIMER

Klement, A. W., Jr., Ayer, D. E. and Rogers, E. B.: Simultaneous Use of Cr^{51} and T-1824 Dye in Blood Volume studies in the Goat. Am. J. Physiol. **181:** 15 (April), 1955.

In this study, red cells were labeled with Cr^{51} and plasma stained with T-1824 blue dye. When red cells were used, the blood volume was 6.1 per cent of body weight. However, the blood volume is 7.35 per cent when blue dye was used as a criterion. Mean total blood volume was 7.05 per cent of body weight.

OPPENHEIMER

Sodi-Pallares, D., Bisteni, A., Medrano, G. A. and Cisneros, F.: The Activation of the Free Left Ventricular Wall in the Dog's Heart. Am. Heart J. **49:** 587 (April), 1955.

This study is a critical attempt to review some o

he more recent experimental studies on ventricular ctivation. The authors state that the spread of ctivation in the subendocardial muscle mass and at east one-half of the thickness of the adjacent free entricular wall, reaches values of 2,000 mm. or nore per second. Differences in results from those of ther investigators depend on: (1) results obtained hrough exclusive use of unipolar lead, (2) erroneous nterpretation of these tracings, (3) failure to take nto account a current of injury produced by the ressure of the exploring electrodes, (4) use of non-atisfactory unipolar leads and (5) interpretation of ncomplete bundle branch block as complete bundle ranch block.

RINZLER

RHEUMATIC FEVER

Seely, J. R., Ely, R. S., Done, A. K., Ainger, L. E. and Kelley, V. C.: Effects of Therapy on Concentration of 17-Hydrocorticosteroids in the Plasma of Patients with Rheumatic Fever. Pediatrics **15:** 543 (May), 1955.

Serial levels in the plasma of 17-hydroxycorticosteroids were obtained in patients with active rheumatic fever under different forms of therapy in addition to bed rest, namely, oral cortisone, intramuscular cortisone, hypophylized corticotropin (ACTH), ACTH-gel, salicylates, and bed rest alone. Elevated levels are found only in the early stage of the disease. The group treated with bed rest alone or salicylates developed no elevation; the group receiving oral cortisone or hypophylized ACTH developed transiently high levels related to dosage level of drug administered and these levels rapidly declined. The group receiving intramuscular cortisone or ACTH-gel showed sustained elevations of these levels. The authors feel that successful hormonal therapy is mediated through sustained high plasma levels of 17-hydroxycorticosteroids.

HARVEY

Salazar-Mallen, M. and Rulfo, J.: On Some Features of Rheumatic Fever and Rheumatic Heart Disease as Seen in the National Cardiological Institute of Mexico. Ann. Int. Med. **42:** 607 (March), 1955.

In Mexico, rheumatic heart disease produces bout one third of the cases of cardiopathy. Considering the rheumatic index, its prevalence is comarable to that found in temperate climates in such ountries as England and the United States. The heumatic morbidity is low in tropical-rainy climate, hereas it is very high in temperate-rainy zones and holds a medium position in dry climate. The reuction of rheumatism since 1947 can be attributed improved living conditions in the Mexican epublic.

WENDKOS

Soloff, L. A. and Zatuchni, J.: Causes of Death in Rheumatic Heart Disease. Relationship to the Incidence of Mitral Stenosis Occurring Alone or with Other Valvular Lesions. Am. J. Med. **18:** 419 (March), 1955.

Of 188,066 admissions to Temple University Hospital and Episcopal Hospital during the years 1945 to 1952 and 1945 to 1949, respectively, 141 patients died from a clinically diagnosed rheumatic heart disease. Of the total admissions, 0.9 per cent entered with a diagnosis of rheumatic heart disease, frequently with associated unrelated illnesses. The cause of death, in decreasing order of frequency, was heart failure (39.7 per cent), acute rheumatic carditis (13.5 per cent), bacterial endocarditis (11.3 per cent), systemic embolism and pre-existing heart failure (9.2 per cent), systemic embolism without heart failure (8.5 per cent) and pulmonary infarction and heart failure (6.4 per cent). In the remaining 11.3 per cent, death was not related to rheumatic heart disease or its sequelae. Diseases, in addition to rheumatic heart disease, were present in at least 39.1 per cent. Acute rheumatic fever or bacterial endocarditis caused all the deaths before the age of twenty and the majority of cardiac deaths in the third decade. Of those who died from heart failure, as many died before as after the age of 50. A clinical diagnosis of isolated mitral valve disease was made in 49.7 per cent but this diagnosis was confirmed at necropsy in but 26.1 per cent. Isolated mitral stenosis was found in only 12 patients (17.4 per cent). Mitral stenosis in combination with other valvular lesions was found in 28 (40.6 per cent). All with systemic emboli, without heart failure, had isolated mitral stenosis, whereas those with failure had predominant combined valve disease. Only four individuals with isolated mitral valve disease had fatal heart failure, two of these had stenosis. Calcification of the mitral valve was found at necropsy in 13.0 per cent, but never occurred in the presence of isolated mitral valve disease.

HARRIS

Bunn, W. H. and Bennett, H. N.: Community Control of Rheumatic Fever. J. A. M. A. **157:** 986 (March 19), 1955.

For several decades an obvious but not well understood relationship has been recognized between β-hemolytic streptococcic infections and rheumatic fever. It is recognized that first attacks of rheumatic fever can be prevented by early and adequate penicillin therapy of streptococcal sore throat in a large percentage of cases and this can be done simply and inexpensively if the person with the sore throat can be identified and if his physician is aware of the importance of correct treatment. One of the approaches to this problem is community education of parents, teachers, school nurses and physicians as has been done in three counties in northeastern Ohio.

KITCHELL

Wedum, B. G. and Rhodes, P. H.: Differential Diagnosis of Rheumatic Fever in Office Practice. J. A. M. A. **157:** 981 (March 19), 1955.

The authors discuss their experiences in the examination of 2,639 children seen in consultation for the presence of active rheumatic heart disease. The totals represent problems encountered by 250 physicians in their practices. The findings, raising the question of presence of rheumatic fever, are (in order of frequency): (1) systolic murmurs, other murmurs and abnormal heart sounds; (2) joint and muscle pain; (3) possible active rheumatic fever or carditis; (4) fever of unknown origin; (5) nosebleeds; (6) restless movements suggesting chorea; (7) unexplained tachycardia; (8) elevated sedimentation rate; (9) possible cardiac enlargement and (10) questionable electrocardiographic findings. Conditions occurring in the normal child may be confused with signs of rheumatic fever. The diagnosis of rheumatic fever and heart disease in children should be made with care. It is sometimes necessary to observe a child for weeks or months before definite diagnosis can be made. Once the diagnosis is established, however, the patient should receive year round penicillin prophylaxis indefinitely and regardless of age.

KITCHELL

Losner, S. and Volk, B. W.: The Fibrinogen Polymerization Test in Active Rheumatic Disease. Am. J. M. Sc. **229:** 371 (April), 1955.

It has been shown that fibrinogen remains preserved in serum when heparin has been given in vivo or added to the blood specimen in vitro. The preservation of fibrinogen in serum has been attributed to interference with polymerization of fibrinogen by heparin. On the basis of this observation the fibrinogen polymerization test was devised in which either 50 mg. of heparin intravenously or 8 μg. per 3 cc. of blood in vitro are used as critical doses to preserve serum fibrinogen. It is believed that this dose will differentiate between normal and accelerated fibrinogen depolymerization. The absence of fibrinogen in serum, two hours after gross coagulation of heparinized blood, has been designated as a positive or abnormal result. The persistence of fibrinogen in serum, two hours after gross coagulation, is a negative or normal result. In a series of 42 patients with active rheumatic processes, the fibrinogen polymerization test was uniformly positive. In 12 normal subjects and 21 control patients, the test was negative. In patients with acute rheumatic fever, this test remained positive, long after other laboratory criteria of activity had returned to normal. The test was unaffected by cortisone administration. The clotting times of heparinized blood from both groups of patients were identical, suggesting that fibrinogen preservation in serum is not due to antithrombic properties of heparin but due to interference with fibrinogen polymerization.

SHUMAN

Wallach, J. B., Lukash, L. and Angrist, A. A.: Multivalvular Involvement in Rheumatic Heart Disease with Particular Reference to Cardiac Surgery. Am. J. M. Sc. **229:** 368 (April), 1955.

In 292 necropsied cases of severe rheumatic heart disease, the incidence of mitral stenosis alone was 58 per cent, aortic stenosis, 11 per cent and combined mitral and aortic stenosis 31 per cent. The figures indicate that the number of patients eligible for cardiac surgery can be considerably increased by surgical attack on multivalvular lesions. Since this estimate is based on pathologic findings, without regard to the clinical status or other criteria, this represents the maximum increment. With respect to antemortem thrombi, mitral stenosis cases have an incidence of 18.6 per cent when the aortic valve is not involved. In cases with the combined valvular lesions, there was an incidence of atrial thrombi of 35.8 per cent. It is suggested that nonbacterial thrombotic vegetations may be a significant source of embolism in cardiac surgery. The potential increase in frequency of embolization during more extensive operative manipulations is stressed.

SHUMAN

Dorfman, A.: The Role of Hormones in Treatment of Rheumatic Fever. Pediatrics **15:** 605 (May), 1955.

This is a review article summarizing the experience over the past four years of the effectiveness of steroid hormones in the treatment of rheumatic fever. The article is well indexed and a good bibliography is presented. The work of many investigators is reviewed. The consensus seems to be that treatment with the steroids results in a more prompt response in the manifestations of rheumatic fever and, in particular, those manifestations of carditis. There is no evidence that cardiac damage is prevented by the steroids. In mild cases, it is felt, salicylates should be used rather than steroids. Lastly, the author feels steroids have no place in the long continued treatment of the chronic rheumatic, because of the lack of effect and potential dangers in the use of the drugs.

HARVEY

Neve, R. A. and Aldrich, R. A.: Urinary and Erythrocyte Porphyrin in Children with Acute Rheumatic Fever. Pediatrics **15:** 553 (May), 1955.

Urinary coproporphyrin levels were measured in 15 children with acute rheumatic fever being treated in the hospital, in 15 hospitalized children without rheumatic fever and in 38 normal healthy ambulatory children serving as controls. There was a significantly higher excretion of coproporphyrin excretion in the rheumatic patients than in the other children. Treatment with salicylates did not alter this coproporphyrin excretion. The free erythrocyte levels of protoporphyrin were normal in all groups of children. Inadequate evidence is presented that the liver is the site of the biochemical disturbance resulting in in-

creased coproporphyrin excretion in acute rheumatic fever.

HARVEY

Done, A. K., Ely, R. S., Ainger, L. E., Seely, J. R. and Kelley, V. C.: Therapy of Acute Rheumatic Fever. Pediatrics **15:** 522 (May), 1955.

This presentation gives results of treatment of 62 children with acute rheumatic fever, 14 were treated with corticotropin (ACTH) and bed rest, 14 with cortisone and bed rest, 21 with salicylates and bed rest and 13 with bed rest alone. (The doses of hormones used were much greater than commonly used and treatment was continued for many weeks.) Prophylactic antibiotic therapy was given to all. All of the patients had signs of myocarditis, heart murmurs and migratory polyarthritis in addition to fever and elevation of the sedimentation rate. In all treated groups, the alleviation of joint symptoms occurred quite promptly, but slightly faster in the hormone treated patients. The untreated group responded much more slowly. The response in fall in temperature to normal was quick in all three groups. The sedimentation rate fell more rapidly in the hormone treated group. Clinical recrudescence of the process was significantly greater in the salicylate treated group than it was in the hormone treated groups. Follow-up studies done three and one-half years after initial treatment, the authors feel, show that less residual damage results when hormones are given.

HARVEY

Lubschez, R.: Identification of Urinary 17-Ketosteroids in Rheumatic Fever. Pediatrics **15:** 537 (May), 1955.

Pooled, 24 hour urine specimens, collected over three days from four nonrheumatic, four rheumatic children who, at the time, showed no clinical evidence of rheumatic fever and from one child with active rheumatic myocarditis, were analyzed for 17-ketosteroids. The technics in measuring these substances were identical with well recognized, previously done determinations made at the Sloan Kettering Institute. These lent themselves to comparisons. It was found that the urinary ketosteroids in rheumatic children (either active or inactive) do not differ from those of nonrheumatic children.

HARVEY

Gilbert-Queraltó, J. Torner-Soler, M. and Balaguer-Vintró, I.: The Electrocardiogram in Mitral Stenosis before and after Commissurotomy. Am. Heart J. **49:** 548 (April), 1955.

A comparative study of the electrocardiogram and the hemodynamic data has been made in 16 cases of mitral stenosis. In eight of them the electrocardiogram variations have been followed after commissurotomy until a maximum of one and one-half years.

Of 12 cases with sinus rhythm, the P wave was abnormal in nine cases before the intervention. In the remaining four cases atrial fibrillation was present. The most important sign of P wave alteration consists in the increase of its duration over 0.10 second, which appeared in the nine cases. Another important sign is the positive-negative diphasism of the P wave in lead V_1. The P wave had a high voltage in six cases, all but one had pulmonary hypertension. The P wave axis was deviated in five cases. The two cases with a deviation toward the left were not accompanied by pulmonary hypertension, while the three cases with deviation toward the right had pulmonary and right ventricular hypertension. The aspect of the electrocardiogram before the operation was classified in four types: normal, border line, right bundle branch block and right ventricular hypertrophy pattern. The normal, border line and right bundle branch block tracings appear in the patients without or with a slight pulmonary hypertension, although the right bundle branch block can also be found in patients with a marked pulmonary hypertension. The tracings with a definite right ventricular hypertrophy pattern appear only when there is a marked pulmonary and right ventricular hypertension. In our cases they appear when the pulmonary systolic pressure is above 60 mm. Hg. After the operation, a transitory appearance of atrial fibrillation was observed in three of eight cases. It appeared generally between the third to the sixth day and disappeared spontaneously in our cases before the first month. The P wave usually modifies itself a short time after the operation, except the high voltage P wave with axis deviation toward the right and the reduction of the negative component of P wave in lead V_1. The first is in relation to the reduction of pulmonary hypertension and the second according to the size of the mitral surface area.

As for the electrocardiogram, in the six cases with right ventricular hypertrophy pattern, this disappeared completely in two cases, while in the other four, the inversion of the R to S ratio and the delay of activation time in lead V_1 became less marked by the following electrocardiogram.

RINZLER

McKusick, V. A.: Rheumatic Restenosis of Mitral Valve. Arch. Int. Med. **95:** 557 (April), 1955.

A case of autopsy-confirmed rheumatic mitral restenosis in a 36 year old, white female is reported. Death from acute nocturnal pulmonary edema occurred 57 months after operation. Smoldering rheumatic activity at the time of valvulotomy and inadequacy of sulfonamide prophylaxis were considered to be leading factors in the restenosis.

BERNSTEIN

ROENTGENOLOGY

Ceballos, J., Calderon, R. and Kargl, O.: The Determination of Individual Enlargement of the Ventricles by Radiologic Methods. Am. Heart J. **49:** 606 (April), 1955.

This paper describes a method for determining the

size of the left and right ventricle by radiologic means and reviews the findings in 115 cases which were checked with the clinical diagnosis, electrocardiographically and in some instances with angiocardiography, surgery or at autopsy. The method involves locating the interventricular septum and then tracing two perpendicular lines to extend to the cardiac shadow in its most convex part. The anterior one represents the width of the right ventricle and the posterior that of the left. The interventricular septum corresponds to a line which follows the heart axis and goes from the posterior margin of the aorta to the inferior portion of the heart shadow where the septum makes a small curve downward and posteriorly to reach the indentation which indicates the ending of the interventricular septum.

RINZLER

SURGERY AND CARDIOVASCULAR DISEASE

Gertler, M. M., Finkle, A. L., Hudson, P. B. and Neidle, E. G.: Cardiovascular Evaluation in Surgery. I. Operative Risk in Cancer Patients with Bundle Branch Block. Surg., Gynec. & Obst. **99:** 4 (Oct.), 1954.

In evaluating the cancer patient with bundle branch block as a surgical risk, one must decide whether the cardiac condition or the malignant lesion is the determining factor of life expectancy. The authors have evaluated 21 patients from a urologic service and 35 from a surgical service, all having cancer and bundle branch block. The average age was 66.3 years and 68.1 years for the urologic and surgical services, respectively.

In evaluating the bundle branch block the authors took into consideration a number of factors. First, the type of block is important. Right bundle branch block, as previously reported, usually offers a better prognosis than left. The best survival records are seen in patients with the S type or indeterminate bundle branch block. Second, the underlying etiology for the bundle branch block is significant. The presence of coronary atherosclerosis offers a more serious prognosis than congenital bundle branch block. Third, abnormal cardiac function resulting directly or indirectly from the bundle branch block bears upon medical evaluation of the problem. This involves an estimation of the presence of congestive heart failure, angina pectoris and cardiac enlargement.

From the present study, no correlation could be made between the type of bundle branch block and outcome of surgery. All types of bundle branch block present no greater risk than the underlying etiologic cardiac disease coupled with the degree of cardiac compensation (as evidenced by cardiac enlargement and congestive heart failure).

No fatalities occurred in this series. Postoperative complications of relatively minor consequence were encountered in 11 men and five women. Shock and hypotension were the most common; these were easily corrected by appropriate therapy. The authors discuss the indications for specific cardiac preoperative preparation and also point out the need and wisdom of complete cooperation between the surgeon and the cardiologist.

DENNISON

Jones, R. E., Donald, D. E., Swan, H. J. C., Harshbarger, H. G., Kirklin, J. W. and Wood, E. H.: Apparatus of the Gibbon Type for Mechanical Bypass of the Heart and Lungs. Proc. Staff Meet., Mayo Clin. **30:** 105 (March), 1955.

Ten consecutive operations, carried out under standard conditions, were included in the experiments performed with a view toward survival of the animal. In each of these, the animal was connected to the Gibbon-type machine for 40 to 60 minutes, during which time the right atrium was opened and the cavae occluded for a 30 minute period. Nine of these 10 dogs survived without discernible ill effects. In the nonsurvivor, death was partly attributed to hemorrhage from a faultily ligated femoral artery. Certain tentative conclusions may be drawn from this group of dogs. First, by means of this apparatus, it is possible to maintain the circulation of the experimental animal without the development of untoward sequelae. Second, when gentle, controlled suction was utilized, no difficulty was encountered in obtaining adequate venous return from the dog. Third, the mixed venous oxygen saturation in these animals was maintained at relatively normal levels, indicating an adequate flow of blood to the tissues. The blood leaving the machine through the artery line was fully saturated with oxygen. Subsequent experiments were performed in which ventricular and atrial septal defects were satisfactorily repaired.

SIMON

Swan, H., Cleveland, H. C. and Blount, S. G.: Technique of Tricuspid and Mitral Commissurotomy. Arch. Surg. **70:** 379 (March), 1955.

The authors reported the results of bilateral valvulotomy in three patients. In each instance the clinical findings suggested the presence of tricuspid as well as mitral stenosis. They pointed out that whereas a significant degree of mitral insufficiency eliminates the possibility of a beneficial result from surgery in mitral stenosis, this does not necessarily apply to triscuspid insufficiency.

In the three operated patients, there was an increased morbidity as compared to individuals undergoing only a mitral commissurotomy. However, the complications eventually cleared up.

ABRAMSON

Bergner, R. P.: Cardiac Arrest: Some Etiologic Considerations with Reports of Seventeen Cases. Anesthesiology **16:** 177 (March), 1955.

Cardiac arrest during an operation may result from factors associated with the anesthesia, the surgery or from underlying or complicating patient disease. The author believes that most instances of primary cardiac arrest are more often caused by anesthetists and surgeons than by anesthetic agents or surgery. In the discussion of the 17 cases of cardiac arrest that comprise this series, he points out that seven cases were the direct result of the anesthetist attempting to "catch up" with the surgical procedure; two cases were partially due to technical errors in the administration of the anesthesia; and three cases were due to errors in judgment in administering an anesthetic agent used. The remaining four cases represented poor-risk patients in whom hazardous operations had to be performed. This group constitutes an "occupational hazard" which must be recognized and accepted. He emphasizes that the treatment of cardiac arrest must be immediate and vigorous and should include artificial respiration, cardiac massage and elimination of the cause of the arrest. After cardiac arrest has been corrected, the original surgical procedure should be delayed or postponed if at all possible.

SAGALL

Shumacker, H. B., Jr. and King, H.: The Use of Pliable Plastic Tubes as Aortic Substitutes in Man. Surg., Gynec. & Obst. **99:** 287 (Sept.), 1954.

The authors were first confronted with the problem of treating a patient with a ruptured abdominal aortic aneurysm. No homologous aortic graft was available at the time. Experiences with the use of finely woven nylon in the repair of experimentally produced atrial and ventricular septal defects had demonstrated that this material was tolerated well within the heart, that its use was not associated with thrombosis and that it became covered with an endothelial membrane. During these experiments it was advantageous to render the nylon tube impervious to blood. This objective was accomplished by placing a thin sheet of nonreactive polythene between two sheets of nylon and ironing the material with an iron adjusted to "wool."

The authors report on the use of the finely woven nylon cloth graft in six cases. There were two deaths in the group, one from a lower nephron nephrosis, the other unexplained. These occurred in the postoperative period. It is significant that peripheral evidence indicated the graft to be functioning in all six cases.

It is obvious that certain advantages will accrue if aortic and aortic bifurcation grafts of plastic material will serve satisfactorily. They are constructed of inexpensive and readily obtainable thin, finely woven nylon cloth. They are easily and quickly prepared. They can be made of any size and shape. Thus a number of them can be made available so the surgeon can select a suitable one at the time of operation. Though thin and pliable, they have great tensile strength. They can be sterilized by autoclaving. They can be sutured to the ends of the vessel by ordinary technics of vascular anastomosis. Experimental observations demonstrate that a strong new fibrous aorta, with a smooth inner lining, is developed about the inert graft from host tissues.

DENNISON

Likoff, W., Berkowitz, D., Denton, C. and Goldberg, H.: A Clinical Evaluation of the Surgical Management of Combined Mitral and Aortic Stenosis. Am. Heart J. **49:** 394 (March), 1955.

An evaluation of the surgical management of combined mitral and aortic stenosis is described in 74 patients. The preoperative clinical and objective findings are compared with those found 3 to 24 months after operation. There was no mortality in combined commissurotomy for uncomplicated mitral and aortic stenosis. The presence of an additional insignificant lesion raises the mortality rate just beyond that of aortic commissurotomy for pure stenosis and to over twice that of mitral stenosis. Two insignificant lesions increase the mortality to almost twice that of aortic commissurotomy and over four times that of mitral commissurotomy. When one or more additional major defects are present, one of every two patients fails to survive. When the dual operation is carried out before the age of 50, the mortality for all groups is 27 per cent. This is three times the risk of aortic or mitral commissurotomy in the same age category. Therefore, the primary indication for combined commissurotomy is the presence of mitral and aortic stenosis which results in significant and progressive abnormal physiology. Additional significant lesions with the possible exception of mitral insufficiency and the presence of congestive heart failure are firm contraindications. Insignificant lesions, an age beyond 50 and a functional class of three or greater add to the operative risk but not the contraindications. A systolic pressure which is persistently below 100 mm. Hg is a poor prognostic sign because it implies decrease in renal flow and filtration, following operation, and serves as a deterrent below the age of 50 and as a contraindication thereafter. As in surgery for other types of rheumatic heart disease, acute rheumatic activity, subacute bacterial endocarditis and associated major disease are contraindications.

RINZLER

Holman, E. and Willett, F.: Results of Radical Pericardiectomy for Constrictive Pericarditis. J. A. M. A. **157:** 789 (March 5), 1955.

Twenty-six patients with constrictive pericarditis have been subjected to radical pericardiectomy. Four patients died; one five days after operation, and one 40 days after operation, both from myocardial failure. One patient died four months after operation (from intestinal obstruction, unrelated to the cardiac

disease), the other patient died 28 months after operation from cardiorenal disease, diabetes and pneumonia. The midline sternal-splitting incision provided easy accessibility to all parts of the heart and contributed greatly to the safety of the operation. Fourteen patients with nontuberculous pericardial thickening are well. Three cases are limited to moderate activity (because of atrial fibrillation, associated congenital pulmonic stenosis and an associated mitral stenosis respectively). Eight patients with tuberculous pericarditis (in six of whom viable tubercle bacilli were cultured) recovered and are well. Only one patient (tuberculous) required a secondary pericardiectomy. The uniformly excellent healing that followed all operations must be ascribed to the full use of antibiotic therapy. Pericardiectomy must be radical to be effective and in order that all critical areas may be liberated the decortication must extend beyond the left border, right border, and lower border, with release of both the inferior and the superior vena cava and the base of the heart.

KITCHELL

Moscovitz, H. L., Gordon, A. J., Braunwald, E., Amram, S. S., Sapin, S. O., Lasser, R. P., Himmelstein, A. and Ravitch, M. M.: The Use of Simultaneous Left Heart Pressure Pulse Measurements in Evaluating the Effects of Mitral Valve Surgery. Am. J. Med. **18:** 406 (March), 1955.

A method for recording the pressure gradient between the left atrium and the left ventricle at the operating table, by inscribing simultaneous pressure pulses in the left heart, is described and recommended as the best method of determining the degree of hemodynamically significant mitral stenosis. The normal filling pressure gradient across the mitral valve approximates zero. The effect of valvulotomy on the elevated pressure gradient in mitral stenosis is to produce a fall of variable degree, depending on the adequacy of the surgical procedure. When this pressure gradient remains high after valvulotomy, relief of the obstruction can be termed inadequate. The method is also of value in the differential diagnosis of mitral stenosis, in aiding the surgeon at the operating table to decide whether sufficient manipulation of the valve has been carried out and in determining whether recurrence of obstruction has taken place in patients previously operated upon for mitral stenosis.

HARRIS

Krook, H., Biorck, G. and Wulff, H. B.: Tricuspid Stenosis and Constrictive Pericarditis In One Patient Successfully Treated by Simultaneous Valvulotomy and Pericardiectomy. Am. Heart J. **49:** 467 (March), 1955.

A case of constrictive pericarditis combined with stenosis of the tricuspid valve is described in a 24 year old male farm worker. Simultaneous pericardiectomy and tricuspid valvulotomy (finger-fracture) were performed, with disappearance of cyanosis, edema, ascites, and the enlarged liver. Microscopic examination of the pericardium did not reveal any specific inflammatory tissue. Since there was no history of rheumatic fever, there remained no clue as to the origin of either lesion.

RINZLER

Desforges, G., Ridder, W. P. and Lenoci, R. J.: Successful Suture of Ruptured Myocardium After Nonpenetrating Injury. New England J. Med. **252:** 567 (April 7), 1955.

The authors describe a case of cardiac rupture due to nonpenetrating trauma suffered in an automobile accident. Massive hemothorax was found to be due to a longitudinal tear 4 cm. in length in the right atrium and superior vena cava at their junction. This tear was closed successfully and recovery followed. This is believed to be the first such case so treated. The authors express the belief that rupture of an intact, healthy myocardium after trauma to the body can conceivably occur only as a result of profound changes in the intrathoracic and intracardiac pressure. It is felt further that the speed with which the atrial pressure changes may be important in producing rupture of the myocardium. It is recommended that a suspicion of cardiac rupture be entertained whenever there has been extensive injury capable of producing chest compression or rapid increase in intravascular venous pressures such as abdominal compression. If the pericardium remains intact the picture of tamponade will predominate; if the pericardium is torn massive hemothorax and evidence of blood loss will result.

ROSENBAUM

McCune, W. S., Raad, A. and Blades, B.: Latex and Thorium Dioxide (Thorotrast) in Treatment of Aneurysms. Arch. Surg. **70:** 583 (April), 1955.

The authors produced experimental aortic aneurysm in 75 dogs, using nitrogen mustard injected into adventitia and media of the vessel and then studied the effect of the local application of various substances to determine which one, if any, would prevent rupture of the lesion. The best results were obtained with a mixture of liquid latex and thorium dioxide. The use of latex alone was not quite as good.

On the basis of the experimental results, latex and thorium dioxide were applied to three large, otherwise inoperable, aortic aneurysms in humans. One of the patients died in the immediate postoperative period of a mesenteric thrombosis, the second survived for two years and died of rupture of a large aneurysm of the aortic arch, while the third was still living two and one-half years after the application of the material.

The authors concluded that a latex-thorium dioxide mixture was a satisfactory coating for sup-

porting large aneurysms which, because of their size, location or the general condition of the patient, could not be treated by resection.

ABRAMSON

Hurwitt, E. S. and Rosenblatt, M. A.: Observations on the Growth of Aortic Anastomoses in Puppies. III. Use of Absorbable Gelatin Sponge (Gelfoam) in Relation to Growth. Arch. Surg. **70:** 491 (April), 1955.

The abdominal aorta of a small series of puppies was divided and united surgically and then the anastomosis was wrapped with absorbable gelatin sponge. The latter step was performed in order to determine whether or not the absorbable gelatin sponge would interfere with the growth of aortic anastomoses.

An increase in the diameter of the anastomosis was consistently obtained but the rate of growth was slightly less than that observed in the control group in which the gelatin sponge was not applied.

It was concluded that when gelatin sponge is used to reinforce vascular suture lines in children, it should be placed as a patch over a particular site rather than wrapped around the entire anastomosis.

ABRAMSON

Mortensen, J. D., Edwards, J. E., Grindlay, J. H. and Kirklin, J. W.: Reinforcement of Fresh Autogenous Venografts to Aorta. Arch. Surg. **70:** 545 (April), 1955.

The authors performed an experimental study in dogs, to determine whether polyvinyl formalinized (Ivalon) sponge could be used as an effective reinforcing agent around fresh autogenous venografts implanted into the aorta. The sponge was wrapped around the segments of jugular vein at the time of implantation.

In the case of fresh autogenous venografts alone, histologic studies revealed that within three months after implantation, an adventitia had developed consisting of vascular connective tissue which mingled with the fragments of adventitia of the original vein. When the sponge was used as reinforcement, the interstices of this material became infiltrated with neutrophilic granulocytes within 72 hours after implantation. Vascular fibrous tissue gradually infiltrated these interstices.

The grafts supported by the polyvinyl formalinized sponge functioned satisfactorily and generally remained remarkably free from tendencies to thrombose, dilate or constrict during a nine month follow-up period.

ABRAMSON

Parsons, H. G. and Holman, E.: Experimental Segmental Pericarditis. Arch. Surg. **70:** 479 (April), 1955.

By means of resection of different portions of the pericardium in dogs and suturing of the retained portion to the great vessels or the chambers of the heart, constriction of various parts of the circulatory system was achieved. When the constriction of the pericardium was limited to the right side of the heart, the peripheral venous pressure rose, cardiac output decreased, and ascites formed. When only the right atrium or the pulmonary veins were involved, none of these changes was observed. However, obstruction of the inferior vena cava to half its size resulted in dilated superficial veins, extensive collateral venous circulation, elevated venous pressure and marked ascites. The ascites decreased, to reappear when the superior vena cava was constricted to one-third its outside diameter.

Constriction of the left side of the heart produced a diminished cardiac output and a narrowed pulse pressure, while the same change limited to the left auricle caused no alteration in hemodynamics.

It was concluded that decortication must include both ventricles, the venae cavae and the auriculoventricular grooves if these structures are found to be invested by the constricting pericardium.

ABRAMSON

Mahorner, H.: The Treatment of Aortic Aneurysms. Surg., Gynec. & Obst. **100:** 110 (Jan.), 1955.

The author reviews the history of the evolution of treatment of aortic aneurysms, pointing out that the modern methods began at the latter part of the nineteenth century with attempts to suture arteries.

The preferred approach to the problem is the use of homologous grafts to replace the excised segment of involved artery. Two procedures which appear most practical in controlllng the circulation while the operation is being performed are: chilling the patient into a stage of hypothermia, during which the circulation and the demand for it are retarded so that complete cross clamping of the upper aorta can be successfully used; and exclusion of the part of the aorta at two levels with clamps of the Potts or Beck type, while a graft is applied around the segment to be removed by two end-to-side anastomoses. In the latter case, the circulation may thus continue through part of the aorta even at the level at which it is partially clamped.

ABRAMSON

Adelman, M. H.: The Anesthetic Management of the Cardiac Patient With a Note on Induced Hypotension. J. Mt. Sinai Hosp. **21:** 355 (March–April), 1955.

The evaluation of every cardiac patient as an operative and anesthetic risk should be undertaken by the internist, anesthesiologist and surgeon. The anesthesiologist must decide on an anesthetic technic that is safest for the patient; i.e., one that avoids (1) emotional excitement before and during surgery, (2) excessive physical exertion during anesthesia, (3) hypoxia, (4) hypercapnea, (5) marked depression or elevation of arterial and venous pressures, (6) diminished coronary blood flow and (7) changes in the irritability of the cardiac muscle.

The two main hazards of general anesthesia to the cardiac patient are hypoxia and respiratory acidosis. Ether is remarkably free of untoward cardiovascular effects, when administered skillfully, having little effect on the contractile force of the heart and on blood pressure. Nitrous oxide and ethylene have no untoward cardiovascular effects, when given with adequate amounts of oxygen, although they are not very potent anesthetics unless used with other agents. The incidence of cardiac arrhythmias during ethylene anesthesia is the lowest of all inhalation agents. Cyclopropane may cause disturbances in cardiac rhythm and should not be used when there is evidence of increased myocardial irritability, conduction defects, and cardiac arrhythmias. Chloroform and ethyl chloride are potent myocardial depressants. Intravenous short acting barbiturates have little or no effect on the cardiovascular system, but are not true anesthetics and therefore have limited usefulness. Local infiltration and field block, where indicated, are safe for the cardiac patient. Low spinal anesthesia is generally safe for the cardiac patient in surgery of the lower extremity, perineum, rectum and bladder, but high spinal anesthesia is contraindicated.

Induced hypotension is used to attain a bloodless operative field, to minimize blood loss and to shorten the operative time. Methods of inducing hypotension include spinal anesthesia, epidural anesthesia, arteriotomy with reinfusion of blood and ganglion blocking agents, the latter being the method of choice, especially the short acting ones such as Arfonad and pendiomide. Indications for induced hypotension include operations in which massive hemorrhage may occur, vascular surgery and neurosurgery. Contraindications include coronary artery disease or severe heart disease, hepatic or renal insufficiency, atherosclerosis, severe anemia, shock and degenerative central nervous system disease.

CORTELL

OTHER SUBJECTS

Segar, L. F., Kashtan, H. A. and Miller, P. B.: Trichinosis with Myocarditis. Report of a Case Treated with ACTH. New England J. Med. **252:** 397 (March 10), 1955.

A man of 40 developed evidence of trichinosis, with signs of myocarditis, 33 days after the ingestion of uninspected pork. The evidence of myocarditis consisted of tachycardia, gallop rhythm, frequent ventricular premature beats and inversion of the T waves in leads V_2, V_3 and V_4 of the precordial electrocardiogram. Within 36 hours after the initiation of treatment with Acthar Gel, these signs of myocarditis cleared. It is believed that ACTH suppresses the inflammatory response of the myocardium to the invasion of the trichinella larvae and that this effect should permit the physician to carry the patient through the phase of greatest danger until the larvae become encysted.

ROSENBAUM

Horowitz, W.: Management of the Pregnant Patient with Cardiac Disease. New England J. Med. **252:** 511 (March 31), 1955.

The author classifies among the unfavorable or poor risk patients, in addition to those with a history of previous congestive heart failure, women with atrial fibrillation, hemoptysis which is felt to indicate pulmonary hypertension due to tight mitral stenosis, active rheumatic fever, subacute bacterial endocarditis, increasing hypertension, striking enlargement of the cardiac chambers, aortic stenosis, coarctation or dissection of the aorta or congenital cardiac disease with cyanosis. The opinion is expressed that it is desirable to terminate the pregnancy as soon as possible after compensation has been restored in a patient in the unfavorable category. Interruption should not be attempted after the sixth lunar month. Prenatal care should include a low salt diet, limiting the weight gain for the entire pregnancy to 20 pounds, supplementing the diet with vitamins, calcium and iron, precautions against heavy physical work and infections and frequent careful check-up examinations. Heart failure, occurring in the prenatal period, is treated in the usual fashion and with venous tourniquets and phlebotomy, if needed, for acute pulmonary edema. The author reports the use of digitalis prophylactically in patients whose cardiac reserve is low. Coarctation of the aorta or dissecting aneurysm is considered specific cardiac indication for cesarean section. Consideration of prophylactic cesarean section is also recommended to avoid a trial of long, arduous labor in a problem case with low acrdiac reserve.

ROSENBAUM

Parr, F. and Schmitt, W.: Silicosis and Circulation. Arch. f. Kreislaufforsch. **22:** 80 (March), 1955.

Hemodynamic studies are reported in 68 cases of silicosis, 27 of which had arterial hypertension. In 40 per cent of the cases, the circulating blood volume was increased in the absence of heart failure. The latter was proven by measurement of the venous pressure (20 to 40 mm. water) and determination of the circulation time (16 to 17 seconds). There was no correlation between increment of blood volume and the various roentgenologic stages of the pulmonary disease. The electrocardiogram showed in the average more right axis deviation than expected with the age of the individual patient, but not to such a degree that it could be related to the lung condition.

The augmentation of circulating blood volume must, according to the authors, be attributed entirely to hypoxia engendered by the disturbance of pulmonary function. Alterations in blood pressure, heart rate and respiration, as observed in exercise tests performed in the course of the study, could, however, be caused by additional latent cardiac failure. In order to demonstrate the latter factor, continuous measurements of the venous pressure subsequent to the exercise test are necessary.

PICK

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

The City of Hope. *Samuel H. Golter.* New York, G. P. Putnam's Sons, 1954. 177 pages, 25 figures. $3.50.

Probleme und Beispiele Biologischer Regelung. *R. Wagner.* Stuttgart, George Thieme, 1954. 219 pages, 38 figures. $7.00. U.S. Agent: Intercontinental Book Corp., 381 4th Avenue, New York.

Einführung in die Biologische Registriertechnik. *Herbert Klensch.* Stuttgart, Georg Thieme, 1954. 222 pages, 142 figures, 8 tables. $7.85. U.S. Agent: Intercontinental Book Corp.

The Ciba Collection of Medical Illustrations. A Compilation of Paintings on the Normal and Pathologic Anatomy of the Reproductive System. Volume 2. Summit, N. J., Ciba Pharmaceutical Products, Inc., 1954. 286 pages, 233 color plates. $13.00.

Ciba Foundation Symposium on The Kidney, Arranged Jointly with the Renal Association. *A. A. G. Lewis, ed. Renal Association, G. E. W. Wolstenholme, ed., Ciba Foundation, Assisted by Joan Etherington.* Boston, Little, Brown & Co., 1954. 333 pages, 125 figures, 25 tables. $6.75.

L'Infarto del Miocardio. *Mario Mattioli.* Ed. 2, Napoli Edizioni Scientifiche Italiane, 1955. 490 pages, 65 figures.

Transactions of the American College of Cardiology, Vol. III, 1953. *Bruno Kisch, Robert P. Glover, and Ashton Graybiel, eds.* New York, The American College of Cardiology, 1954. 259 pages, 80 figures, 13 tables.

Collaque sur la Cure de Sommiel. *Under the direction of G. Nora and M. Sapir.* Paris, Masson & Cie, 1954. 238 pages, 21 figures, 8 tables. $4.00. Available through Intercontinental Book Corp.

L'Hypertension portale. Le Dumping Syndrome. IV^e Congrés de l'Association des Societes Nationales Europeennes et Mediterraneennes de Gastro-Enterologie. Paris, Masson & Cie. 1954. 458 pages, 161 figures. $11.50. Available through: Intercontinental Book Corp.

Electrocardiografia. *Emilio Araya.* Buenos Aires, Lopez & Etchegoyen, S.R.L., 1955. 425 pages, 222 figures.

Das Transversale Schichtverfahren. *Alfred Gebauer and Alfred Schanen. With technical assistance by F. Wachsmann.* Stuttgart, Georg Thieme, 1955. 313 pages, 349 figures. $23.20. U.S. Agent: International Medical Book Corp.

Endothelium. Its Development, Morphology, Function and Pathology. *Rudolf Altschul.* New York, Macmillan Co., 1954 157 pages, 9 figures. $3.50.

Segundo Curso de Cardiologia. *Eduardo Coelho, with the collaboration of others.* Lisbon, Imprensa Medica, 1954. 337 pages, 129 figures, 7 tables, 1 graph.

Cardiac Injury Resulting from Effort or Trauma. Clinical and Legal Aspects. *Ernst P. Boas.* Ann Arbor, Mich., Edward Brothers, Inc., 1955. 113 pages, 1 table.

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Surgery of the Heart. *Charles P. Bailey.* Philadelphia, Lea and Febiger, 1955. 998 pages, 671 figures, 1452 illustrations. $25.00

Transactions of the Second Congress of the International Society of Angiology. *Henry Haimovici, ed.* Bruxelles, Imprimerie Medicale et Scientifique (S.A.), 1954.

Diagnostic Electrocardiographique. *Andre Jouve, Jacques Senez, Jean Pierron. Preface by Prof. Charles Laubry.* Paris, Masson et Cie., 1955. 448 pages, 242 figures. $15.85. Available through: Intercontinental Book Corp.

Accidents Nerveux des Cardiopathies Congenitales Cyanogenes. *Pierre Corone.* Paris, Amedée Legrand & Cie., 1954. 233 pages.

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Modern Medical Monographs: Potassium Metabolism in Health and Disease. *Howard L. Holley, and Warner W. Carlson.* New York, Grune & Stratton, Inc. 1955. 144 pages, 11 illustrations. $4.50.

Clinical Diagnosis. *Elmer G. Wakefield.* New York, Appleton, 1955. 1605 pages, 135 illustrations. $22.50.

A Textbook of Physiology. *John F. Fulton.* Ed. 17, Philadelphia, Saunders, 1955. 1275 pages. 600 illustrations. $13.50.

Current Therapy. *Howard F. Conn, ed.* Other Consulting Editors. Philadelphia, Saunders, 1955. 692 pages. $11.00.

Balistocardiographia Clinica. *Sergio Alvarez Mena.* Cuba, La Habana, 1955. 320 pages, $7.50.

Ciba Foundation Symposium on Chemistry and Biology of Pteridines. *G. E. W. Wolstenholme and*

Margaret P. Cameron, eds. Boston, Little, Brown & Company, 1955. 416 pages, 143 illustrations. $8.00.

Ion Exchange and Absorption Agents in Medicine. *Gustav J. Martin.* Boston, Little, Brown & Co., 1955. 307 pages, 26 illustrations. $7.50.

Clinical Disorders of Hydration and Acid Base Equilibrium. *Louis G. Welt.* Boston, Little, Brown & Co., 1955. 215 pages. $6.00.

Rutin and Related Flavanoids. *John Q. Griffith, Jr., Charles F. Krewson, and Joseph Naghski.* Easton, Pa., Mack Publishing Co., 1955. 242 pages.

Fluoroscopy in Diagnostic Roentgenology. *Otto Deutschberger.* Philadelphia, W. B. Saunders Co., 1955. 729 pages, 888 illustrations, 523 figures, $22.00.

Mitral Stenosis. *Knud Henning Olesen and Ejnar Munksgaard.* Copenhagen, Ejnar Munksgaards Forlag, 1955. 211 pages. Dan.kr.18,-

Differential Diagnosis of Internal Diseases. *Julius Bauer.* Revised Ed. 2, New York, Grune & Stratton, Inc., 1955. 1004 pages, 66 illustrations. $15.00.

Hematology. *Cyrus C. Sturgis.* Ed. 2, Springfield, Charles C Thomas, 1955. 1192 pages. $19.50.

Management of Addiction. *Edward Podolsky.* New York, Philosophical Library, 1955. 408 pages. $7.50.

Heart Disease. Its Diagnosis and Treatment. *Emanuel Goldberger.* Ed. 2, Philadelphia, Lea & Febiger, 1955. 767 pages. $12.50.

Should the Patient Know the Truth. A Response of Physicians, Nurses, Clergymen and Lawyers. *Samuel Standard and Helmuth Nathan.* New York, Springer Publishing Co., Inc., 1955. 158 pages. $3.00.

Annual Review of Medicine, Vol. 6. *David A. Rytand, ed. and John Anderson, asso. ed.* Stanford, Calif., Annual Reviews, Inc., 1955. 420 pages. $7.00.

BOOK REVIEWS

Principles of Internal Medicine. *Tinsley Harrison, ed.* Ed. 2, New York, The Blakiston Company, 1954, 2 volumes, 1791 pages, 206 figures, 149 tables. $21.00. Student volume ed. $16.00.

The second edition of Harrison's *Principles of Internal Medicine* continues the original physiologic approach to disease mechanisms. The student is made aware of the multiple facets of disease and their effect on the patient as an individual, as the transition from normal physiology to disturbed function and morbid anatomy is traced in accurate, precise and easily readable sequence. Cross reference prevents much of the repetition found in text books of this magnitude.

The chapters dealing with cardiovascular matters have been expanded to advantage. Many have been extensively rewritten and new subjects have been added. Of particular interest is a new amply illustrated chapter on congenital heart disease which places more emphasis on pathophysiology, catheterization data, and x-ray findings than on simple pathologic anatomy. Equally significant is the revised and lengthened section on hypertension which has been broadened to include the pharmacology of the newer therapeutic agents. Points of authority questioned in the earlier addition have been modified to embrace divergent views where such exist. An instance can be cited in the new description of the mechanism of gallop rhythm.

The entire cardiovascular section shows evidence of modernization along lines of recent investigational trends. More stress is placed on vector theory in the description of electrophysiology and there is added a short, concise section on ballistocardiography. The paragraphs dealing with systolic murmurs at the apex of the heart are now more aptly titled "apical systolic murmurs" as opposed to "mitral insufficiency" in the earlier edition.

This textbook of medicine continues to rank high in its field and should be in the library of every student and physician who desires more from a fundamental text than a catalog of symptoms and therapeutic measures.

T. M. McMillan, III

Peripheral Vascular Diseases. *Edgar V. Allen, Nelson W. Barker and Edgar A. Hines, Jr.* Ed. 2, Philadelphia, Saunders, 1955. 825 pages, 316 figures. $13.00.

This is an excellent book, and the most inclusive treatise in the field. The second edition has been thoroughly revised and contains up-to-date concepts and descriptions of the diseases and of most of the new trends in therapy. The illustrations are well-chosen. The comprehensive text and index combine to make it a good reference work. Diseases of the arteries and veins of the extremities, and diseases of the aorta are considered in detail. There is a short treatise on diseases involving the vena cava. Diseases of the following vessels are scarcely touched upon: cerebral, coronary, mesenteric and portal, so presumably are not considered "peripheral". I have only a few criticisms, most of them minor.

There is some need of further editing. There are several inconsequential typographical errors. Throughout the book there is considerable repetition and, though some of it is good teaching, some is unnecessary. There are a few examples of confusion. For instance, the subject of skin temperature in arteriovenous fistula is introduced as "warmer distal to the fistula than the skin of the companion member," and in the next paragraph "it may be normal or decreased in a portion of the extremity considerably distal to the fistula." Also, after reading the section on therapeutic materials that depress prothrombin, there is unnecessary confusion as a result of reporting "prothrombin time" and especially in using the term "T". Prothrombin should be reported by the laboratory only as "percent of normal prothrombin activity," and only this term should be used by the physician when dealing with the clinical problem. Per cent of normal prothrombin activity of the unknown is, of course, derived in the laboratory from measurements of prothrombin time obtained by using the same thromboplastin in the case of the unknown as in the case of dilutions of "normal" plasmas as standards. The term "T" is not clearly defined. It is apparent by the examples given that the figure (number) given along with "T" is the per cent of normal prothrombin activity. The term "T" adds nothing of value, and if used, a physician might get the idea that the figure (number) given with it refers to prothrombin *time*, which could be dangerous. Furthermore, the use of a 300 mg. dose of Dicumarol, after previous doses have been given, is excessive. In the use of Dicumarol, heparin or some other quick-acting anticoagulant should be begun promptly until such time as the Dicumarol becomes effective.

The medical and surgical sections of the book need closer integration. For instance, the subject of thoracic aneurysms is in one section where mention is made of treatment by some surgical procedures but not by aortic grafts, whereas thoracic aortic grafts are described in a later section. The authors seem hesitant, when listing appropriate surgical treatments in the medical section of the book, to use arterial grafts for peripheral arterial occlusions and for peripheral arterial aneurysms, but in the surgical section this procedure is described and advocated for these purposes. It is then a bit confusing to find the surgeon, two pages later describing in detail the excision of a popliteal aneurysm without replacement by graft.

The section on *Temperature Studies* of the skin is difficult to follow and should better be combined with the following section concerning *Reflex Vasodilatation*. The description of variations in skin temperature later in the first section should appear earlier. In neither of these sections is the concept of temperature "gradient" presented, the important concept that flow of relatively warm blood warms the skin exposed to the relatively cool environment. The work of Landis and Gibbon or that of Pickering should be quoted, and the "vasodilatation test" they outlined should be described.

Two points concerning intermittent claudication are unsatisfactory. The use of tissue extracts is advocated, but there is no reference to a critical paper regarding their being of any value. The term "arteriospastic claudication" is referred to too briefly, if indeed this syndrome does exist.

There are some statements with which I do not agree. Although some of them are qualified by discussion in other parts of the book, when taken in their immediate context they are misleading. Page 146, under *Frostbite*: "There is no essential difference clinically between trench foot or immersion foot and the 'slow-freeze' type of frostbite." Page 224: "Intermittent claudication may be described as . . . cramp . . . in the region of certain muscles which develops only after a period of exercise." Page 237, under *Diagnosis of Arteriosclerosis Obliterans*: "Occlusion of small arteries distal to the ankle by arteriosclerosis without occlusion of the larger arteries proximal to the ankle is extremely rare in our experience and for practical purposes need not be considered". Page 298: "Long-term anticoagulant therapy with Dicumarol or other common compounds is theoretically of some value . . . for patients who have thromboangiitis obliterans." Page 562: "The presence of deep chronic venous insufficiency with its various manifestations of edema, eczema, induration and ulceration is not a contraindication to treatment by stripping." Page 565: "In our experience ligation of the deep veins has not solved the problem of deep vein insufficiency, but removal of the superficial veins and ligation of incompetent perforating veins plus adequate elastic support have given excellent results." Page 621. "The results of treatment by continuous intravenous injection of heparin have been favorable." Page 646, under *Postural Exercises*: "The affected limb is elevated with the patient lying in bed, to from 60 to 90 degrees above the horizontal, being allowed to rest upon a support for from 30 seconds to 3 minutes, the period of time being the minimum amount of time necessary to produce blanching or ischemia." Although this is quoted from Buerger's own work, this degree of elevation causes an excessive loss of arterial flow. Page 650, in describing the use of typhoid vaccine in thromboangiitis obliterans, there is no caution against doses sufficient to cause chills. Page 699, 189 and 191: Intermittent positive and negative pressure therapy is ascribed to Herrmann and Reid; that this increases blood flow was first demonstrated by Landis and Gibbon, and their names should be added.

I have read this book in detail and have reported all I think at fault. It remains, however, an excellent book which every one responsible for the care of patients having these diseases should own.

HUGH MONTGOMERY, M.D.

AMERICAN HEART ASSOCIATION, INC.

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1956 AHA ANNUAL MEETING AND SCIENTIFIC SESSIONS

Those wishing to present either papers or scientific exhibits at the 1956 Scientific Sessions of the American Heart Association in Cincinnati next fall must make application before May 15. The Scientific Sessions are scheduled in conjunction with the 32nd Annual Meeting of the Association, October 27–31.

For persons interested in offering papers, the May 15 date is the deadline for submitting abstracts. Papers intended for presentation must be based on original investigation in or related to the cardiovascular field. The abstracts must be submitted in triplicate on forms obtainable from the Medical Director of the Association. Abstracts should not exceed 300 words and should contain in summary form the results obtained and the conclusions reached.

This year's Scientific Sessions are to be held at the Cincinnati Music Hall and space will be available for an enlarged section devoted to scientific and technical exhibits. Requests for space for scientific exhibits and applications can also be obtained from the AHA Medical Director (44 East 23 Street, New York 10). All exhibit applications will be acted upon by the Program Committee of the Scientific Council as soon as possible after the May 15 closing date for applications.

AHA MAKES WIDE DISTRIBUTION OF RHEUMATIC FEVER CRITERIA

Distribution by the Association of reprints of the statement, *Jones Criteria, (Modified) for Guidance in the Diagnosis of Rheumatic Fever,* to 183,000 practicing physicians and 25,000 medical students has been instituted in cooperation with the National Heart Institute and the American Medical Association.

The statement was first published in September, 1955, issue of the AHA's monthly bulletin for physicians, *Modern Concepts of Cardiovascular Disease.* It is a revision of the widely accepted rheumatic fever diagnostic criteria originally drawn up by the late T. Duckett Jones, M.D. The modified criteria are intended as a guide to the physician which will help him to avoid the dangers of either overdiagnosis or underdiagnosis of rheumatic fever.

The mailing to the nation's physicians also includes a wallet card designed by the National Heart Institute which provides, in abbreviated form, the streptococcal treatment schedules recommended by the Committee on Prevention of the Association's Council on Rheumatic Fever and Congenital Heart Disease.

Additional copies of the Jones Criteria statement can be obtained from local Heart Associations or from the American Heart Association, 44 East 23 Street, New York 10.

DR. CRISMON HEADS RESEARCH COMMITTEE

Jefferson M. Crismon, M.D., Professor of Physiology at the Stanford University School of Medicine, Palo Alto, Calif., has been elected Chairman of the Research Committee of the Association's Scientific Council. Dr. Crismon succeeds Howard B. Burchell, M.D., Mayo Clinic, Rochester, Minn.

A. C. Corcoran, M.D., Cleveland Clinic, Cleveland, was chosen as Vice Chairman of the Research Committee.

AHA REPRESENTATIVES TO ATTEND TWO INTERNATIONAL CONGRESSES

The Association has accepted invitations to send representatives to two international cardiologic congresses this year. They are the Second European Congress of Cardiology, to be held in Stockholm, September 10–14, and the Inter-American Congress of Cardiology, Havana, November 11–17.

NEW YORK HEART ASSOCIATION PLANS SCIENTIFIC SESSION

The Annual Spring Scientific Session of the New York Heart Association is scheduled for Tuesday, April 24 at the New York Academy of Medicine.

The session is designed to give investigators in the cardiovascular field, particularly younger investigators, an opportunity to report on their research. To insure the greatest possible participation, papers are to be limited in length to 10 minutes each. Persons interested in making presentations are invited to submit by February 14 abstracts of no more than 300 words to the Medical Director, New York Heart Association, 485 Fifth Avenue, New York 17.

ARTERIOSCLEROSIS STUDY SOCIETY NAMES DR. CORCORAN

A. C. Corcoran, M.D., Cleveland Clinic, Cleveland, O., was elected President of the American Society for the Study of Arteriosclerosis at the Society's recent annual meeting in Chicago. Dr. Corcoran succeeds Louis N. Katz., M.D., Chicago.

Also elected by the arteriosclerosis group were Charles F. Wilkinson, Jr., M.D., New York, as Vice President and O. J. Pollak, M.D., Dover, Del., as Secretary-Treasurer.

The Society has also announced that the deadline for submission of abstracts for presentations at its 1956 Annual Meeting is May 31. The 1956 meeting will be held in Chicago's Palmer House, November 11–12. Factual abstracts should be submitted to Dr. R. Gordon Gould, Program Chairman, P. O. Box 1663, Los Alamos, N. M.

HEART ELECTROPHYSIOLOGY CONFERENCE, FEBRUARY 16–17

A conference on the Electrophysiology of the Heart, bringing together many distinguished clinicians and research investigators from the United States and abroad, will be held at the Barbizon-Plaza Hotel in New York City, Thursday and Friday, February 16–17, under the joint auspices of the Section on Biology of the New York Academy of Sciences and the National Heart Institute of the U. S. Public Health Service.

The Conference, which is to be dedicated to the memory of Frank N. Wilson, M.D., will be chaired by Hans H. Hecht, M.D., University of Utah. Sections will be held on the following subjects:

Cellular Events During the Cardiac Cycle, Spread of the Impulse through Cardiac Muscle, Anomalous Atrio-Ventricular Excitation (panel), Cardiac Recovery, the U-Wave and After Potential in Cardiac Muscle (panel), Distribution of Electrical Potentials in Volume Conductors and Analysis of the Surface Electrocardiogram.

A general round table discussion on Electrocardiographic Theory and Practice, beginning at 8:15 P.M., Friday, will include Doctors K. S. Cole, National Institutes of Health; Howard B. Burchell, Mayo Clinic; Hans H. Hecht; Charles E. Kossman, New York University; Louis N. Katz, Michael Reese Hospital; George E. Burch, Tulane University; and Eugene Lepeschkin, University of Vermont.

Among the distinguished foreign participants will be Doctors W. Weidmann, Berne, Switzerland; H. Schaefer, Heidelberg, Germany; D. Durrer, Amsterdam, Netherlands; D. Sodi-Pallares, Mexico City; and H. C. Burger, Utrecht, Netherlands.

Sessions will be conducted throughout the day starting at 9:00 A.M. and continuing through the evening with luncheon and dinner gatherings. The conference will be open to all interested professionals. Additional information and programs may be obtained from Mrs. Eunice T. Miner, Executive Secretary, New York Academy of Sciences, 2 East 63 Street, New York 21.

NEW ECG COURSE AT MICHAEL REESE

A new 12-week course in electrocardiographic interpretation is scheduled to begin on February 8 at the Michael Reese Hospital in Chicago. The course, to be given by Louis N. Katz, M.D., Director of the Cardiovascular Research Institute at Michael Reese, is designed for graduate physicians. It will be conducted every Wednesday evening from 7:00 to 9:00 P.M. Further information may be obtained from Mrs. Ana Rose, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

PRACTICAL CARDIOLOGY COURSE SCHEDULED IN HOUSTON, MARCH 14–17

A course in Practical Bedside Cardiology will be conducted at the University of Texas

Postgraduate School of Medicine in Houston, March 14–17, by Samuel A. Levine, M.D., Clinical Professor of Medicine at Harvard University Medical School. The course will be under the joint sponsorship of the Texas Postgraduate School of Medicine, the Baylor University College of Medicine and the Houston Heart Association.

Featured will be materials designed to assist the physician in the recognition and management of the most common cardiovascular problems. Further information may be obtained from the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25.

MEETINGS CALENDAR

Feb. 10–11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6.

Feb. 13–16: Sectional Meeting, American College of Surgeons, Philadelphia. American College of Surgeons, 40 East Erie St., Chicago 11, Ill.

March 19–22: Eighth Annual Scientific Assembly of the American Academy of General Practice, Washington, D. C. Armory. Secretary, American Academy of General Practice, Broadway at 34th, Kansas City 11, Mo.

March 24–25: American Psychosomatic Society, Sheraton Plaza Hotel, Boston. Theodore Lidz, 33 Cedar St., New Haven 11.

April 3: Third Microcirculatory Conference, Hotel Schroeder, Milwaukee, Wisconsin. Dr. G. P. Fulton, Dept. of Biology, Boston University, 675 Commonwealth Ave., Boston 15.

April 4–6: American Association of Anatomists, Milwaukee. Normand L. Hoerr, 2109 Adelbert Rd., Cleveland 6.

April 9–12: 30th Annual Congress, International Anesthesia Research Society, Miami Beach. Dr. R. J. Whitacre, 13951 Terrace Road, Cleveland 12.

April 11–13: American Surgical Association, White Sulphur Springs, W. Va. R. Kennedy Gilchrist, 59 E. Madison St., Chicago 3.

April 15–16: American Society for Artificial Internal Organs, Atlantic City. Peter F. Salisbury, M.D., Institute for Medical Research, Cedars of Lebanon Hospital, 4751 Fountain Avenue, Los Angeles 29.

April 15–20: American Society for Pharmacology and Experimental Therapeutics, Atlantic City. C. C. Pfeiffer, Emory University School of Medicine, Emory University, Ga.

April 15–20: American College of Allergists, New York. F. W. Wittich, 401 Marquette Bank Bldg., Minneapolis 2.

April 15–21: American Society for Experimental Pathology, Atlantic City. Cyrus C. Erickson, 874 Union Ave., Memphis 3.

April 26–28: American Association of Pathologists and Bacteriologists, Cincinnati. Edward A. Gall, Cincinnati General Hospital, Cincinnati 29.

April 27–28: American Gastroenterological Association, Atlantic City. H. Marvin Pollard, University Hospital, Ann Arbor, Mich.

April 29: American Federation for Clinical Research, Atlantic City. William W. Stead, V.A. Hospital, Minneapolis 17.

April 30: American Society for Clinical Investigation, Atlantic City. A. O. DeWeese, 515 East Main Street, Kent, O.

May 1–2: Association of American Physicians, Atlantic City. P. B. Beeson, Yale University School of Medicine, New Haven 11.

May 3–4: American Geriatrics Society, Malford W. Thewlis, 25 Mechanic St., Wakefield, R. I.

May 29–June 3: Society of American Bacteriologists, Houston. J. H. Bailey, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

ABROAD

March 6–9: Ciba Foundation Symposium on Influence of Ionizing Radiation on Cell Metabolism (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London, W.1.

March 26–28: Ciba Foundation Symposium on The Biophysics and Biochemistry of Viruses (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London, W.1.

April 28–May 5: Third International Conference on Health Education, Rome, Italy. Lucien Viborel, Secretary-General of Union, 92 rue Saint-Denis, Paris 1er, France.

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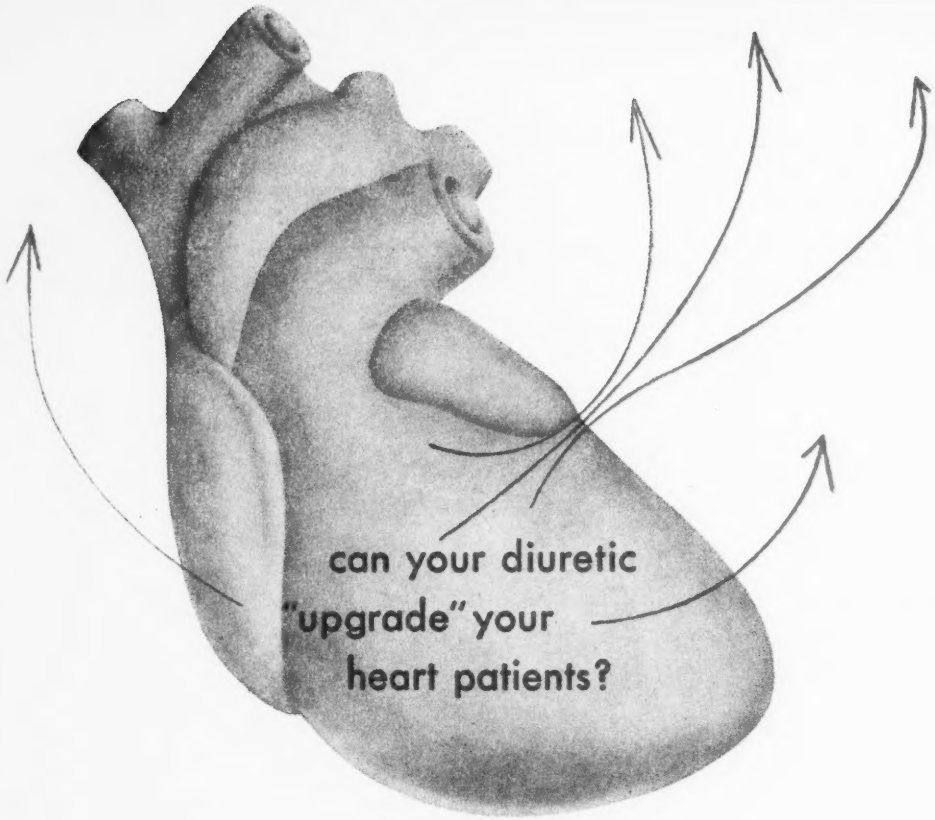

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